

The Lung
as a Mirror
of Systemic Disease

By

ELI H RUBIN, MD

Professor of Clinical Medicine
Albert Einstein College of Medicine
Yeshiva University

Director of Pulmonary Diseases
Bronx Municipal Hospital Center

Attending Physician
Division of Pulmonary Diseases
Montefiore Hospital

Consulting Physician in Pulmonary Diseases
Lebanon and Morrisania City Hospitals

New York New York



CHARLES C THOMAS • PUBLISHER
Springfield • Illinois • USA

CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue Springfield, Illinois, U S A

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD, OXFORD ENGLAND

Published simultaneously in Canada by
THE MYERSON PRESS TORONTO

This book is protected by copyright. No
part of it may be reproduced in any manner
without written permission from the publisher

Copyright 1956 by CHARLES C THOMAS • PUBLISHER

Library of Congress Catalog Card Number 56 6494

Printed in the United States of America

*This book is dedicated to the memory of my teachers
the late Dr Maurice Fishberg and
the late Dr Max Pinner*

Acknowledgments

I AM DEEPLY indebted to my colleagues at Montefiore Hospital, especially to Drs Robert G Bloch, Louis Leiter and Harry M Zimmerman, respective Chiefs of the Pulmonary, Medical and Laboratory Divisions, for making available to me the wealth of clinical and postmortem material which furnishes the background of this book. Dr Ruth Lubliner was particularly helpful in supplying data and illustrations of surgical pathology. The Department of Roentgenology was most cooperative. Much of the information bearing on specific problems in differential diagnosis and treatment is drawn from medico surgical study of patients treated jointly by Dr Morris Rubin and myself.

A number of the cases cited have been published previously by associates and members of the staffs of the several hospitals with which I am presently or have been affiliated. Proper acknowledgment is made to the authors and the sources in conjunction with the items drawn from the various publications. I would like to express my personal thanks to the authors and publishers for allowing me to reproduce some of the printed matter. Drs Sol Biloon, John Dawson and Alfred Goldman kindly allowed me to publish several cases of unusual interest.

My profound thanks are due my secretary, Miss Lillian Kahn, for typing the manuscript, checking the bibliography, arranging the index and putting up with many demands above and beyond the line of duty. Mr Antol Herskovitz, medical photographer to Montefiore Hospital, did an excellent job in his specialized field. The tedious chore of correcting proof was ably handled by Bertram M and Susan Gesner, and Isaac M Rubin. Finally, I would like to express my thanks to the publisher, Charles C Thomas for the high grade of craftsmanship, which went into the finished product.

E H R

Preface

IN THE FOLLOWING pages a number of diseases are described in which the lungs may mirror what is happening in other parts of the body. The sequence in which the various diseases are presented is primarily for orientation purposes. It is not intended to serve as a classification in the generally accepted sense of the term since it is often impossible to draw sharp distinctions between one group of diseases and another. Several of the conditions to be described cannot be fitted at present into any classification because they are too fluid to be pigeon holed into specific compartments. With the development of new techniques in diagnosis and treatment, diseases and syndromes are constantly being discovered, occasionally rediscovered, and new ones created. This involves an endless reclassification. As aptly stated by Bohrod, "There is no such thing as a correct classification, there are only useful classifications."

This volume is a segment of medicine with emphasis on disseminated diseases which may be associated with pulmonary lesions as part of the basic disturbance. This explains why considerable description is included of the disease as a whole as well as of the pulmonary lesions. In fact, it will appear at times that more space is allotted to the former than the relatively insignificant lesions in the lungs would seem to warrant.

In justification of certain liberties taken, it bears emphasis that the chest x-ray the key stone of diagnosis of pulmonary diseases, is a window not a portrait and often mirrors passing events. One is also mindful of the fact that in apparent rarity, once recognized, often becomes commonplace. Certainly, for every patient with rare or bizarre pulmonary lesions, discovered in specialty practice, many times the number pass through the offices of general practitioners, and even hospital wards, with their diverse either unrecognized or misdiagnosed. It is hoped that this book will alert the physician to the wealth of information obtainable in a chest x-ray provided the latter is viewed in broad perspective.

Thesis

ROUTINE \times RAYS of the chest of apparently healthy individuals are a constant reminder that a silent chest does not necessarily contain healthy lungs and that a noisy chest need not connote serious disease. The presence or absence of disease can be established only by a chest \times ray, the findings viewed in the light of the patient's history, physical signs and pertinent laboratory tests. Occasionally the chest \times ray reveals abnormal markings of a type and distribution which are suggestive of these being the manifestations of a systemic disease. In such the chest \times ray may be the first to draw attention to the presence of a widespread disturbance which might otherwise escape detection. Or else the information obtained may be of additional help in differential diagnosis. In either case the lung may serve as a mirror of what is going on in organs and tissues of the body not accessible to direct examination.

Although roentgenography and its various modalities occupy a key position in chest diagnosis and will be featured in the following pages, it would be foolhardy to minimize the value of other means of investigation. A history obtained by the physician, a thorough physical examination and the necessary laboratory tests including bronchoscopy, bronchography and when indicated lung biopsy are as essential in arriving at a diagnosis as are the roentgen findings. In fact there are occasions when the physical examination is more informative than the chest \times ray findings and the history superior to both. However in the diagnosis of obscure systemic disease with pulmonary lesions of the type to be discussed in these pages, physical signs are usually lacking and one may have to resort to all available diagnostic measures and the true nature of the disease may still remain elusive.

Insofar as roentgen diagnosis *per se* is concerned, there is nothing pathognomonic about lights and shadows in a chest \times ray. An area of density may represent consolidation caused by neoplasm, pneumonia, tuberculosis or a transient atelectasis caused by temporary obstruction of a bronchus. A circumscribed area of translucency may represent a cavity caused by abscess, tuberculosis, neoplasm or lung cyst. The abnormal roentgen markings assume added significance when viewed on a background of what the physician knows of the patient's family and past history, occupation, travels as well as the physical and laboratory findings. The black and white shadows then assume various shadings. With experience, the presence of a particular disease may be suspected or diagnosed with a high degree of accuracy on the basis of the roentgen findings alone. A definitive diagnosis *ab initio* requires confirmatory evidence.

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

Broadly speaking diseases affecting the lungs may be grouped into one of three categories (1) *Primary Diseases* These include developmental defects new growths traumatic injuries and similar conditions The majority of the acute bacterial and viral pneumonias pulmonary suppurations primary pulmonary neoplasms and tuberculosis typify this group (2) *Secondary Diseases* These include pulmonary emboli metastatic malignancies and so called terminal pneumonias (3) *Concomitant Diseases* In these the respiratory tract is involved either initially or in the course of systemic diseases as an active more or less co equal participant These pages are concerned primarily with the last mentioned

When the lungs are involved as part of a systemic disease the following are noteworthy (1) a symmetrical distribution of lesions in both organs (2) a vascular or perivascular pattern of abnormal lung markings and (3) a tendency toward pleural implication The first and second elements are related to the fact that the pulmonary involvement in most systemic diseases is either within or along blood vessels and/or lymphatics The third is due to the fact that the pleura is richly supplied with blood vessels and lymphatics

The pulmonary changes giving rise to abnormal roentgenologic patterns are a composite of (1) normal bronchovascular markings which vary with the age sex occupation and body build of the individual also the conditions under which the roentgen examination is made (2) physiologic and pathologic changes within the air containing units of the lungs which largely determine the radiotranslucency of the affected parts and (3) specific architectural alterations in the way of fibrosis emphysema consolidation or necrosis as well as associated reaction in pleura lymph nodes and adjacent structures In toto the various elements mentioned endow the lights and shadows in the chest x ray with certain qualitative and quantitative characteristics which immediately bring to mind certain possibilities to be considered in differential diagnosis

A disease may manifest itself in the lungs in diverse manner and dissimilar diseases in comparable manner The pulmonary changes may assume the configuration of prominent hilar densities accentuation of bronchovascular markings diffuse fibrosis small or large air cysts miliary or nodular infiltrations patchy or massive consolidations or multiple cavities with or without accompanying pleural effusion More often there is a combination of the aforementioned Yet these several patterns may be the result of a single or a limited number of agents On the other hand diffuse interstitial fibrosis may be the end stage of viral pneumonia allergic pneumonia sarcoidosis scleroderma chronic pulmonary congestion and other diseases Cystic changes may be associated with pituitary disease histiocytosis tuberous sclerosis and other diverse conditions At least fifty abnormal states may give rise to miliary or nodular foci It would take us too far afield to enumerate the diseases which may give rise to pulmonary consolidation cavity formation or pleural effusion The totality of the picture depends on the type of tissue involved the duration of the disease and the intensity of the pathological process As the disease progresses or becomes chronic and recrudescents the causative agent plays an increasingly lesser role as far as determining the final picture

THESIS

There are times when one has the impression that the changes in the lungs as depicted in the chest x ray are in keeping with the presence of a systemic disease, yet one may be unable to demonstrate organ or tissue involvement outside of the chest. This state of affairs is exemplified in instances of diffuse interstitial fibrosis, cystic lung and other obscure conditions currently being met with increasing frequency. It may be speculated that in some the pulmonary changes represent the end stage of a disease at one time widespread in others the lungs may be momentarily the shock organs of a systemic disease, the nature of which is obscure. We have learned by analogy that sarcoidosis was originally described as a dermal disorder, in time, it was recognized as a systemic disease and now is often found in the lungs and regional lymph nodes without demonstrable involvement of other organs. One of the purposes of this book is to indicate the possibilities of similar eventualities with respect to other diseases.

Contents

	<i>Page</i>
<i>Acknowledgments</i>	vii
<i>Preface</i>	ix
<i>Thesis</i>	xi
<i>Chapter</i>	
1 Chest Roentgenography in Mass Surveys	3
Introduction	3
Mass Chest X ray Surveys	3
Tuberculosis case finding	3
Cancer case finding	5
Heart disease case finding	6
Miscellaneous diseases discovered in chest x ray surveys	7
Multiple or multiphasic screening	7
Chest X ray Surveys of Selected Population Groups	8
Armed service personnel	8
Medical students and nurses	11
Pre employment groups	9
Vulnerable ethnic groups	9
Inmates of mental institutions	9
Routine chest x rays in general hospitals	9
Routine chest x rays in clinics	14
Routine Chest X rays and the Private Practitioner	15
Bibliography	16
2 Diseases of Metabolism	18
Introduction	18
Hypertrophic Pulmonary Osteoarthropathy	18
Diabetes and Pulmonary Infections	21
Physiological considerations	21
Diabetes and pulmonary tuberculosis	22
Diabetes and nontuberculous pulmonary infections	23
Cystic Fibrosis of the Pancreas and Pulmonary Infections	25
Introduction	25
Etiology	25
Clinical features	26
Pathological features	27
Roentgenology	27
Bibliography	29

<i>Chapter</i>	<i>Page</i>
3 Diseases of Metabolism (Concluded)	31
Histiocytosis with Pulmonary Involvement	31
Introduction	31
Endogenous lipid pneumonia	32
Gaucher's disease	35
Niemann-Pick's disease	35
Letterer-Siwe's disease	37
Eosinophilic granuloma of bone	39
Eosinophilic granuloma of the lung	40
Pulmonary lesions in the histiocytoses	40
Roentgenology of pulmonary lesions in histiocytosis	41
Amyloidosis of the Lungs	43
Metastatic Calcification of the Lungs	47
Introduction	47
Etiology	47
Pathology	48
Roentgenology	49
Bibliography	50
4 Diseases of the Blood	52
Introduction	52
Pulmonary Diseases Associated with Unusual Blood Findings	52
Tuberculosis	52
Malignant neoplasms	53
Sickle Cell Anemia	54
Pulmonary Hemosiderosis	57
In association with mitral stenosis	57
Idiopathic pulmonary hemosiderosis	58
Hemosiderosis due to iron overload	60
Polycythemia	62
Hemorrhagic Diseases	63
Leukemia	63
Myeloma	65
Infectious Mononucleosis	66
Bibliography	68
5 Allergic Diseases	71
Introduction	71
Tissue Changes in Allergy	71
Bronchial Asthma	72
Clinical features	72
Roentgenology	73

CONTENTS

<i>Chapter</i>	<i>Page</i>
Pulmonary Infiltrations and Eosinophilia	75
Introduction	75
Transitory pulmonary infiltrations and eosinophilia (Oeffler's syndrome)	76
Severe forms of pulmonary infiltrations and eosinophilia	79
Tropical pulmonary eosinophilia	82
Bibliography	83
6 Allergic Diseases (Concluded)	86
The Collagen Diseases	86
Interrelationship of the collagen diseases	86
Polyarteritis Nodosa with Pulmonary Involvement	87
Pathology	87
Pathogenesis	87
Clinical features	88
Pulmonary lesions	90
Rheumatic Pneumonia	95
Pulmonary Lesions in Rheumatoid Disease	96
Diffuse Interstitial Fibrosis of the Lungs Hamman Rich Syndrome	101
Pathogenesis	101
Clinical features	103
Bibliography	106
7 Diseases of the Skin and Mucous Membranes	110
Introduction	110
Allergic Dermatitis	110
Erythema Multiforme	112
Erythema Nodosum	113
Disseminated Lupus Erythematosus	114
Introduction	114
Clinical features	115
Pathology	116
Pulmonary lesions	116
Roentgenology	118
Mycosis Fungoides	121
Neurocutaneous Diseases	122
Tuberous sclerosis	123
Von Recklinghausen's disease (neurofibromatosis)	126
Bibliography	130
8 Diseases of the Skin and Mucous Membranes (Continued)	134
Diseases of the Skin and Malignant Tumors	134

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

<i>Chapter</i>	<i>Page</i>
Scleroderma	135
Pathology	136
Clinical features	136
Roentgenology	137
Dermatomyositis	139
Acanthosis Nigricans	142
Scleredema	144
Sjogren's Disease	144
Bibliography	145
9 Diseases of the Skin and Mucous Membranes (Concluded)	147
Sarcoidosis	147
Introduction	147
Incidence and distribution	147
Pathology	148
Etiology	150
Diagnosis	151
Intrathoracic sarcoidosis	158
Treatment	161
Bibliography	164
10 Pulmonary Manifestations of Certain Abdominal and Metastatic Diseases	167
Pulmonary Manifestations of Abdominal Diseases	167
Introduction	167
Diseases of the diaphragmatic region	167
Diseases involving abdominal viscera	174
Pulmonary Manifestations of Metastatic Diseases	178
Introduction	178
Pathways of pulmonary metastases	178
Pulmonary embolization	180
Roentgenology of metastatic pulmonary lesions	183
Bibliography	187
11 Pulmonary Manifestations of Cardiovascular Diseases	189
Introduction	189
Cardiopulmonary Dynamics	189
Pulmonary Hypertension	190
Physiological considerations	190
Roentgenology	191
Pulmonary Arteriosclerosis	197
Pulmonary Congestion and Edema	193
Physiological considerations	193

CONTENTS

<i>Chapter</i>	<i>Page</i>
Clinical features	194
Roentgenology	194
Azotemia with Pulmonary Manifestations	196
Etiologic considerations	196
Roentgenology	198
Hydrothorax	200
Cavernous Hemangioma of the Lung	201
Clinical features	201
Roentgenology	203
Pulmonary Embolism and Infarction	203
Etiologic considerations	203
Clinical features	205
Roentgenology	206
Bibliography	207
12 Diagnosis The Changing Scene	211
Introduction	211
Changing fashions in medicine	211
Implications of an aging population	211
Implications of the changing character of diseases	212
Implications of changing forms of treatment	212
Diagnosis	213
Clinical history	213
The physical x-ray examination	217
Bibliography	227
13 Diagnosis Symptoms and Signs	221
Introduction	221
Cough	221
Expectoration	222
Hemoptysis	222
Chest pain	223
Dyspnea	225
Physical Exploration of the Chest	226
Inspection	226
Palpation	226
Percussion	226
Auscultation	227
Bibliography	227
14 The Chest X-ray Anatomical and Technical Considerations	229
Introduction	229
Normal Anatomy and Developmental Anomalies	229

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

<i>Chapter</i>	<i>Page</i>
Thoracic cage	229
Diaphragm	231
Medastinum	232
Hilus	233
Lungs and fissures	233
Terminal lung radicles	241
Bronchi and bronchopulmonary segments	242
Röntgen Techniques	249
Fluoroscopy	249
Röntgenography	250
Bibliography	253
15 Pitfalls in Röntgen Diagnosis	256
Introduction	256
The Normal Chest	256
Pitfalls in Diagnosis	257
Intrinsic errors	257
Subjective errors	260
Inherent errors	262
Bibliography	262
16 Laboratory and Exploratory Aids	264
Introduction	264
Examination of the Sputum	264
Bacteriological findings	264
Examination for tubercle bacilli and other bacteria	264
Examination for fungi parasites and other abnormal agents	265
Exfoliative cytology	267
Examination of the Blood	268
The erythrocyte sedimentation test	268
Cytological findings	269
The I E test	269
Skin Tests	270
Tuberculin skin test	270
Kveim skin test	271
Skin tests in fungous diseases	271
Chest Aspiration	272
Bronchoscopy	273
Needle Biopsy of the Liver	273
Prevalene Lymph Node Biopsy	276
Lung Biopsy and Other Surgical Explorations	276
Bibliography	281
<i>Index</i>	283

*The Lung
as a Mirror
of Systemic Disease*

Chest Roentgenography in Mass Surveys

Introduction

CHEST X RAY surveys of apparently healthy individuals were initially introduced as a means of finding tuberculosis but it soon became apparent that nontuberculous chest diseases including neoplasms bronchiectasis pneumonias suppurations cardiac abnormalities developmental defects and the pulmonary manifestations of various systemic diseases may also be detected in this manner. Chest x ray surveys have been most fruitful in the detection of tuberculosis in vulnerable segments of the population such as American Indians and Negroes in industries associated with occupational dust hazards in colleges armed forces establishments diagnostic and prenatal clinics penal and mental institutions and more recently general hospitals.

The introduction of photofluorography by Manoel de Abreu in 1936 utilizing small films has made the mass x ray survey an invaluable tool for case finding. The results obtained in the examination of armed forces personnel during World War II were so gratifying that routine chest roentgenography was soon widely adopted by various public and private health agencies.

The incorporation of a phototimer (Morgan) and the development of a 70 mm apparatus has intensified the use of photofluorography for mass surveys. The basic feature in the mechanism involves a built in photo cell which scans the screen fluorescence created by radiation through the central lung field. The mechanism automatically times the exposure necessary to produce films of any desired density. This assures uniformity in chest radiographs a desideratum in comparing films of the same individual.

The photoroentgen unit is installed either as stationary equipment or as a mobile tractor trailer unit with a self contained power generator. According to one recent estimate approximately fifty million small films were taken from 1946 to 1950 inclusive in the course of chest x ray surveys conducted by various public health agencies in the United States. This number does not include the many standard sized films taken by physicians in their offices the countless numbers taken in clinics and hospitals and the many retake films when screening examinations reveal abnormal findings.

Mass Chest X Ray Surveys

TUBERCULOSIS CASE FINDING

The value of chest x ray screening of a community depends on the percentage of the population covered by the survey and the effectiveness of the follow up of those suspected of having disease. The minimum age of persons examined in general surveys is usually fifteen years. However children are included if there is a history of tuberculosis contact. A major weakness in

mass x ray surveys is the fact that although the screening may include as high as 80 per cent of a community the 20 per cent omitted is apt to have a proportionally larger number of persons with abnormal chest findings. Those who have reason to suspect that all is not well with them are more likely to stay away. This feature of mass radiography is well illustrated in a study conducted by the Ohio University Student

Health Service In the participating or volunteer group, tuberculosis was found in 0.11 per cent, in the "straggler" group the incidence was 1.19 per cent, or approximately ten times higher. Since it is a common practice to project the same prevalence rates of tuberculosis and other chest diseases found in an examined group to the unexamined group, the sources of error in this type of figuring are obvious. It is also well known that elderly persons do not respond to appeals to submit to chest x-rays as do younger ones. Possibly this is due to the fear of the former that should the chest x-ray reveal disease their jobs might be at stake.

As mentioned, the results of mass x-ray surveys parallel the thoroughness of the follow-up of disease suspects. An abnormality found in the chest which cannot be verified adds little to the value of the procedure. On the whole, mass x-ray screening brings to light many suspects but comparatively few with disease of clinical significance. Furthermore, in view of the decreasing incidence of tuberculosis, the cost of finding "positive" x-rays in mass surveys is increasing and the law of diminishing returns is coming into play. Greater efforts will undoubtedly be made in the future to examine the more vulnerable segments of the population. Increasing emphasis will be placed on the findings of tuberculin positive reactors in children. The younger the child with a positive tuberculin test, the more likely is one apt to find a source of infection at home. In the case of infants under two years of age the chances of finding a household source of infection is more than 90 per cent. It may be mentioned at this point that lately tuberculosis is being discovered much more often in persons over fifty years of age than in younger age groups, especially in males. The old "seed bags" will continue to be a source of contagion for some time to come.

As an example of an ambitious undertaking in a community-wide chest x-ray survey, one may cite the Los Angeles X-Ray Project. In a county of about three million inhabitants fifteen years of age or over, one half responded and were x-rayed satisfactorily (Table 1). Unknown cases of ac-

TABLE 1

FINDINGS ON CONFIRMATORY ROENTGENOGRAMS IN
LOS ANGELES CHEST X-RAY SURVEY COMPRISING
1,867,201 PERSONS OF WHOM 64,745 WERE ASKED
TO RETURN AND 54,648 COMPLIED

Essentially negative	14,344
Evidence of old healed disease	9,216
Tuberculosis	18,785
Other chest disease*	
including 3,500 neoplasm suspects	5,646
Cardiovascular disease	6,657
	<hr/> 54,648

From Guiss. *Cancer*, 8:219, 1955.

tive tuberculosis were discovered in 1.08 per thousand. The extent of involvement, in cases of active disease, was minimal in 30 per cent and either moderately or far advanced in 70 per cent. Drolet, who reported these statistics, makes the pertinent comment that mass surveys do not necessarily find the majority of active cases in the early stages of the disease. A similar city-wide survey was conducted in Minneapolis. Of approximately 500,000 inhabitants, 301,513 of the adult population were examined in a period of sixteen weeks. Of those examined, 6,375 were found to have significant lesions. These were referred to private physicians and clinics for further study. A preliminary report of the results was made available of the findings in 3,228 cases. The final diagnoses included (1) 261 persons with active pulmonary tuberculosis, 1,859 persons with inactive or arrested tuberculosis, and (2) 1,108 persons with a variety of nontuberculous diseases (275, cardiac, 122, cancer and 711, "other" conditions).

Community-wide surveys have been conducted in other metropolitan areas, including Erie County and Niagara Falls, New York, Muskogee County, Georgia, Seattle and Tacoma, Washington, Boston and Worcester, Massachusetts, Washington, D.C., and Denver, Colorado. With the cooperation of the United States Public Health Service, 22 such chest x-ray surveys were completed by 1953. Community surveys on less ambitious scales have also been conducted in various parts of Europe. Insofar as the detection of pulmonary diseases are concerned, and tuberculosis in particular, the results vary to some extent with the composition of the popula-

tion. On the average, between 2 to 3 per cent, at most four, of those examined are found to have abnormal chest x-ray findings requiring additional investigation. One per hundred (1.0 per cent) is found to have lesions suspicious of tuberculosis and on further study, this percentage is reduced to 0.1 per cent (one per thousand) with clinically significant diseases. The changing scene in tuberculosis in recent years will undoubtedly be reflected in considerably reduced morbidity rates in the future.

Physicians engaged in x-ray surveys repeatedly draw attention to the fact that community chest screening surveys disclose, in addition to tuberculosis neoplasms and cardiovascular suspects, as well as large numbers with "miscellaneous" conditions. Gould found sixty-six different categories of chest lesions revealed in mass x-ray surveys. Many would not have come to light or would have been discovered in advanced stage if not for roentgenography. In view of the decreasing importance which mass surveys will be occupying in the future in the detection of tuberculosis, it may be worthwhile to discuss briefly the value of this technique in the discovery of pulmonary neoplasms and heart disease. The large "miscellaneous" group of diseases has, as yet, attracted little attention because of the complexity of the problem involved in the follow up and final analysis of such cases. A major objective of this book is to draw attention to the "miscellaneous" or "other chest disease" group, an untapped source of material for future study.

CANCER CASE FINDING

Chest x-ray surveys are instrumental in the discovery of many cases of benign and malignant intrathoracic neoplasms. Guiss in a tabulated summary of ten surveys, found the incidence of possible tumors, detected in chest x-rays, to be 0.8 per 1,000 persons examined. The Los Angeles survey, previously mentioned, disclosed 3,500 chest tumor suspects. In 329, in whom the presence of tumor was confirmed, the disease was found malignant in 246 and benign in eighty-three. An additional number had metastatic lesions (108), goiter (464) and benign

tumors not treated (298) (Guiss, cited by Drolet).

In a chest x-ray survey in Boston, 536,012 persons were examined. Suspicious tumors were found in 398. In thirty-nine the presence of primary bronchiogenic carcinoma was proved, in thirteen the diagnosis was presumptive. Metastatic pulmonary tumors were found in nineteen. The largest number, 275, fell into a miscellaneous group comprising eighty-one cases of tuberculosis, forty-two other infections, fifty-one mediastinal lesions, fourteen chest wall lesions, thirteen diaphragmatic lesions, ten vascular lesions, forty-seven others and seventeen "no disease." McNulty draws attention to the thirty-nine patients with proved primary carcinoma. Twenty-one, or 55 per cent, were resected but only 5 or 13 per cent, were alive and apparently well three years after the date of the original survey film. Guiss reported a "three year cure rate" of the resected cases in the Los Angeles survey, previously cited, of 35.8 per cent, a considerably higher figure than that generally obtained in non-survey groups. This reflects the inclusion of many patients with early, asymptomatic disease.

Guiss notes that of the 3,500 tumor suspects discovered in the Los Angeles survey, only 9 per cent of lung cancers was found in the age group under forty-five years (Table 1). He estimates that were the survey restricted to males more than forty-five years of age, the number of lung cancers would have increased four- to five-fold. As an indication of the effectiveness of the survey, in discovering bronchiogenic carcinoma, is shown by the fact that only twenty-seven of those surveyed who were to die of lung cancer that year were not discovered by the single microfilm, in contrast to the 213 picked up. Butasmuch as 11 per cent were missed, chest x-rays should be repeated twice a year for greater effectiveness.

The question arises whether carcinomas found in the course of mass surveys are more "curable" than those encountered in private practice and whether such tumors can be discovered in sufficiently large numbers to warrant consideration of the mass chest survey as a practicable means of pulmonary cancer control. Since, at present, re-

section is the best treatment available the earlier the disease is discovered and excised the better the prospects of survival. Resection is the treatment of choice for every unexplained mass in the chest especially in persons of the cancer age providing there are no contraindications to surgery. This obviously involves exploratory thoracotomy and resection of many relatively benign circumscribed masses. But this is a small price to pay since disease occupying space in the chest is best removed under any condition unless there are definite contraindications. Garland estimates that photofluorographic screening procedures applied to the general population have led to the detection of about ten cases of bronchiogenic carcinoma per 100 000 persons examined. But if the procedures were restricted to males over forty five and conducted every six months the yield should reach about fifty cases for 100 000.

In a survey of 156 724 people Gowen and Frank reported the discovery of 307 with findings suggestive of malignancy. Follow up of these suspects led to the diagnosis of fourteen with proved carcinoma the majority well advanced. The report by Churchill on bronchiogenic carcinoma discovered in the San Diego survey is particularly instructive. Of 739 000 persons examined carcinoma was correctly diagnosed in twenty of whom seventeen died. In the following two years an additional twenty four in whom the disease was not detected in the survey died of bronchiogenic carcinoma. The average time from the screening to the onset of symptoms in the undetected group was nine months. The symptom free period corresponds closely with that found by Buchberg, Lubliner and myself in a study of 443 patients with fatal carcinoma of the lung proved at autopsy. The duration of life from the time of onset of striking symptoms was 14.7 months from the time of appearance of objective findings 9.1 months.

In view of the fact that only a small percentage of patients can be cured after symptoms develop it is obvious that screening once a year is too long an interval in which to discover symptomless carcinoma of the lung. Persons of advanced age need to be examined at least twice a year. In the

final analysis the diagnosis and treatment of carcinoma of the lung is largely the responsibility of the general practitioner. The physician must be impressed with the importance of taking a chest x ray as part of every complete health examination. In the case of men past forty years of age with unexplained symptoms referable to the chest failure to include a chest x ray is indefensible. Even in presumably clear cut cases of transient atelectasis or resolving pneumonia or pneumonitis of whatever cause follow up x rays should be taken until there is complete resolution of the process. Only in this manner will cancer of the lung be discovered in resectable stages. Recent reports on resectional surgery for malignant neoplasms expressed in five year survivals indicate results approaching 70 per cent twice as good as those reported only a few years ago.

HEART DISEASE CASE FINDING

The Boston survey previously mentioned revealed some interesting information relative to the finding of previously unknown cardiac disease. Rutstein and co workers reported observations on the validity of mass chest x ray surveys in detecting heart disease. Each film was subjected to two independent readings one by readers utilizing usual chest x ray survey techniques where the primary interest is the finding of tuberculosis and a second by a group of radiologists working in pairs who were solely interested in finding abnormalities in the size and shape of the silhouette of the heart and great vessels. All persons whose shadows were classified as abnormal by either or both groups of readers were then requested to return to a special clinic staffed by cardiologists for confirmatory studies.

Considerable variations were found in the yield of abnormal films in the two studies due to differences in training and experience of the readers in the interpretation of x ray shadows of the heart and great vessels. Those who read the films only for heart disease contributed almost three times as many abnormal films as did those who read the films for all chest abnormalities with primary emphasis on tuberculosis. The total yield of verified heart disease was 1.67 per cent.

A comparable study in which all the films were read once only by a survey team for all possible chest abnormalities including those of the heart and great vessels yielded 0.23 per cent with verified heart disease. It would seem therefore that although the small film may be used as a heart disease case finding procedure the value of such screening depends in the final analysis on a careful examination of each cardiac suspect. For this reason as will be discussed later, routine chest x rays of patients admitted to general hospitals and clinics are much more fruitful.

MISCELLANEOUS DISEASES DISCOVERED IN CHEST X RAY SURVEYS

Mass surveys include large numbers of suspects with undiagnosed chest disease. Later chapters will deal at greater length with some of the conditions found among this miscellaneous group and the methods by which a diagnosis may be established in some of the suspects.

It might be pertinent at this point to emphasize a weakness in chest roentgenography as applied to chest x ray surveys which is not sufficiently appreciated by those engaged in mass undertakings. Suspicious lesions discovered in routine roentgenography and which are later found to be due to errors in technique or interpretation or after additional studies are finally judged as being of no clinical significance may be a cause of much worry on the part of the person and family concerned. The several days perhaps weeks it takes before a verdict is reached is a period of stress which few individuals can bear with equanimity. It is therefore important that persons requiring additional studies be examined as expeditiously as possible. Furthermore the ones being examined should be told that suspicious lesions which may be found on routine roentgenography will more often than not turn out to be of no clinical significance and that when they are invited for follow up examinations it need not necessarily signify that disease has been found.

An additional drawback to mass chest x ray surveys is the false sense of security it may engender on the part of those examined as well as on the part of the physician when the report is

made that no abnormalities were found. A negative report means that no demonstrable abnormalities were discovered at the time of the particular examination. It does not guarantee that the lungs will remain immune to disease in the future.

MULTIPLE OR MULTIPHASIC SCREENING

In recent years attempts have been made to incorporate chest x rays taken during routine health examinations in multiple (multiphasic) screening programs. The specific purposes for such undertakings are case finding as well as health education. The method involves the use of two or more simple laboratory tests or procedures applied on a mass basis to determine presumptive evidence of incipient disease or defect. This definition of the nature of multiple screening agreed upon at the National Conference of Chronic Diseases in 1951 does not imply that the particular examinations are in the nature of a diagnostic study no more than is the simple chest x ray of a pulmonary disease. The procedures included in elaborate multiple screening programs are in addition to a chest x ray, a serologic test for syphilis, a hemoglobin determination, an erythrocyte sedimentation test, blood sugar and urine tests, an electrocardiogram, tests for sight and hearing defects, height and weight measurements, Papanicolaou smear examination for tumor cells, and other refinements depending on the medical laboratory and administrative facilities available. The most commonly used tests are chest x rays, serologic tests for syphilis and blood sugar determinations. The more ambitious projects even include a self screening history.

In a review of multiple screening published by the Council on Medical Service of the American Medical Association (November 14, 1953) the advantages as well as the objectionable features are discussed. Among the many objections the following have been voiced. A medical production line type of examination by machine cannot exclude or detect all incipient diseases, also that it may engender a false sense of security in those in whom abnormalities are not found, also that it may cause undue apprehension and

expense for those who are found to have false positive results" It has also been claimed that "the physician has no opportunity to secure an intimate knowledge of the patient" and that there is "no opportunity for an appraisal of the negative group by a physician" Probably the most important defect lies in the fact that "most of the tests that are employed do not possess even an approximately precise value or measure that, on the one hand may indicate that a finding is within physiological limits or, on the other hand, is really indicative of a disease process"

Among the major advantages of a multiple screening program, it is pointed out, are that it offers "an excellent preliminary procedure to any form of examination by reducing the cost and time factors thereby making it possible to extend periodic examinations to significantly larger groups of the population" It is claimed, furthermore, that "multiple screening program is an aid to making people health conscious and seems to stimulate the desire for regular check ups, and that "as a program of prevention, multiple screening has caused a large number of ap-

parently well persons who were not aware that they might have a progressive disease to consult their physicians"

In summarizing the results of nine major projects, totalling more than a million persons screened, Kurlander and Carroll estimated that approximately 50,000 or 5 per cent of the number were found to have disease and/or major abnormalities previously unrecognized In several of the projects, the yield was as high as 10 per cent These investigators emphasize the fundamental differences between screening and diagnosis The former attempts only to select high prevalence groups through the application of standardized tests to numbers of people with the full realization that there will be errors in the form of false positives and false negatives Diagnosis, on the other hand, establishes or rules out disease through a synthesis of the most complete and accurate information available about a particular individual While each of these processes is appropriate in its place, they cannot be used interchangeably

Chest X-Ray Surveys of Selected Population Groups

ARMED SERVICE PERSONNEL

World War II provided illuminating data on the lung findings of approximately 18,000,000 presumably healthy persons In an analysis of a sample of about 200,000 registrants, Morse found that 1 per cent had disqualifying chest disease of which 0.3 per cent had active pulmonary tuberculosis The relatively small number found with nontuberculous disease and the comparatively large number with tuberculosis was undoubtedly due to the age group of the registrants By the same token, the lungs of these individuals had not as yet sustained the wear and tear of life which explains the small percentage found with nontuberculous pulmonary disease The nontuberculous rejections, based chiefly on the roentgen findings, comprised thirty-five different categories

MEDICAL STUDENTS AND NURSES

Tuberculosis developing in the course of train-

ing of medical students and nurses is a serious problem The lowered incidence of this catastrophe in this group in recent years is due partly to the decline of tuberculosis in the general population and partly to the institution of precautionary measures including (1) tuberculin testing and chest roentgenography of all matriculants and at intervals during the course of training, (2) increased use of chest x-rays in hospital and clinics enabling the discovery and segregation of those found tuberculous, (3) the adoption of contagious technique, (4) a more judicious use of tuberculosis clinical and autopsy material in teaching and (5) the establishment of student health departments in universities and colleges BCG vaccination in tuberculin negative reactors and the employment of city bred elderly nurses in tuberculosis institutions, is necessary in most cases because of the shortage of recent graduates, have helped materially in lessening the incidence of tuberculosis among the most exposed group of the population

CHEST ROENTGENOGRAPHY IN MASS SURVEYS

PRE EMPLOYMENT GROUPS

Chest roentgenography is being used with increasing frequency in pre employment examinations. Many states are adopting legislation liberalizing Workmen's Compensation Laws respecting tuberculosis, silicosis and other occupational hazards. This makes it all the more important for employers to discover chest disease in prospective employees which might become compensable. In many cities those employed as food handlers, beauticians and in department stores are required to have periodic x rays of the chest. Teachers and school employees are receiving special attention in this respect. The results of routine chest x rays of workers in low paid industries as well as indigents and recipients of public relief serve to emphasize the important role which the socioeconomic factor plays in tuberculosis.

VULNERABLE ETHNIC GROUPS

A major health problem in the United States is the high incidence of tuberculosis in several ethnic groups of the population notably Negroes, Puerto Ricans and American Indians. Pinner and others believe that a true racial genetic difference exists among various racial segments. The course of the disease and its response to treatment among white and non white groups support this assumption. Undoubtedly contributing factors are present in the unfavorable economic status and living conditions of these people. Although the prevalence of tuberculosis as indicated by tuberculin testing and recent x ray surveys is showing a steady decline, the morbidity and mortality rates among the segments of the population mentioned remain considerably higher than in the general population.

INMATES OF MENTAL INSTITUTIONS

Approximately 600,000 persons in the United States are in institutions receiving care for mental illnesses. Approximately one half of all the patients hospitalized in the country. Chest x ray surveys of inmates of mental institutions reveal a high incidence of tuberculosis. In fact the rate is higher in this group than in the most vulner-

able groups of the population at large. Because of the uncooperativeness of mental patients, difficulties are encountered in the diagnosis and treatment of disease so that repeated chest x ray examinations are necessary. Among patients with dementia praecox, the prevalence of tuberculosis is particularly high, probably because such patients stay longer in institutions and have therefore greater opportunities of developing the disease.

Oechsli reported the results of chest x ray examinations of 25,914 mental patients in seven California hospitals. The study revealed 8.75 per cent of previously unsuspected reinfection type pulmonary tuberculosis and a tuberculosis death rate of over 600 per 100,000. Other investigators have reported similar high morbidity and mortality rates. The true prevalence of tuberculosis in mental institutions is not known because of various laws and regulations which hinder effective case finding programs. Equally important is the fact that a high incidence of tuberculosis is found among employees of mental hospitals and to a lesser extent among employees of institutions for mental defectives. Tuberculosis in mental institutions is a serious problem and comparatively little has been done toward its solution. Proper management involves a chest x ray of every inmate on admission and periodic surveys of all inmates because one has to depend almost entirely on the x ray in the detection of the disease. Effective treatment of pulmonary tuberculosis in patients of mental institutions involves intensive use of antimicrobial medication and resection of localized disease. Halfway measures are not enough.

ROUTINE CHEST X RAYS IN GENERAL HOSPITALS

The routine use of roentgenography for the detection of chest diseases in patients entering general hospitals has not received the wide adoption the procedure merits. All too often chest x rays are taken of such patients days or weeks after admission or when indicated a contingency which may or may not arise and which it does after loss of valuable time. The fact is not sufficiently stressed that a hospitalized pa-

tient with undiagnosed active pulmonary tuberculosis is a source of danger to others including physicians, nurses and other hospital personnel. On the other hand, a patient with a nontuberculous chest disease may be under treatment for a relatively minor ailment while the more serious illness remains undiagnosed. The patient may leave the hospital with disease undetected which might have been treated effectively.

In 1934, Hodges made a test of the utility of routine chest x-rays of all patients during fourteen consecutive working days. The examinations were of patients entering the clinic as well as the hospital. After the films had been processed they were put away. At the end of three months they were re-examined and compared with the hospital records to see whether or not the examinations might have been helpful in diagnosis. It was found that a gross error of omission had been made once every day during the fourteen day period. Realizing that one could not afford to make an error of that extent routine photofluorography was introduced in the hospital beginning in 1941. Over a span of seven years a total of 176,304 admission survey examinations were made including 6,285 examinations of hospital employees. Of the total number examined 94 per cent were considered on the initial review to be sufficiently abnormal to require further study. The figure of 94 per cent remained constant month by month throughout the seven years. On the basis of periodic samplings it was found that the percentage of clinically important chest abnormalities among the survey groups shrank from 94 per cent to 57 per cent when the initial abnormality was more carefully evaluated by other means of investigation.

Oatway, in a survey of the status of routine chest x-raying in 539 general hospitals in the United States as of September 1948, found that 247 hospitals or 66 per cent had routine chest x-rays taken of patients on admission and of these comparatively few included all the admissions. It should be mentioned that the directory of the American Medical Association lists approximately 4,600 general hospitals and a minority of

these provide routine chest x-ray of hospital admissions.

As recently as 1950 Porter, in a survey of the hospitals of New York City, found only ten of 138 institutions to have a program of x-raying patients on admission. These ten institutions accounted for 65 per cent of all the patients admitted to the 138 hospitals; approximately the same percentage as that found by Oatway. Since it is estimated that 30,000,000 persons are treated yearly in the general hospitals of the United States, it is obvious that these institutions harbor large numbers of individuals with undetected chest disease. Since the discovery of the pulmonary manifestations of systemic disease, the topic of our discussion is directly related to the problem of routine chest roentgenography of hospital admissions; it may be pertinent to cite our experience at the Morrisania City Hospital. This project initiated in 1948 was the first of its kind established in the Department of Hospitals of the City of New York.

The case finding project at the Morrisania City Hospital was instituted with the following objectives: (1) to determine the prevalence of pulmonary tuberculosis in patients admitted who were unaware of their disease; (2) to protect physicians, nurses, patients and other hospital personnel from contact with unknown cases of tuberculosis; (3) to discover the presence of nontuberculous chest diseases; (4) to provide a teaching medium for physicians, house staff and medical students; (5) to determine the value of routine miniature roentgenographic examination of the chest as an auxiliary to standard equipment; and (6) to help establish procedures which might serve as a pattern for other hospitals.

Through the generosity of the Bronx Tuberculosis and Health Committee, a 70 mm photofluorographic unit was installed in quarters adjacent to the admitting room of the hospital. Miniature x-ray films are taken routinely of all patients admitted to the wards excepting those in critical condition. If an x-ray is not taken on admission every effort is made to take one while the patient is in the hospital or upon leaving the institution. Patients attending the prenatal clinic

TABLE 2

H. R. 1556-2 (4-52)- OMI sets 566025(53)

THE CITY OF NEW YORK
DEPARTMENT OF HOSPITALS
MORRISANIA CITY Hospital

ADMISSION X-RAY REPORT

Date _____

☐ In Patient _____ (Service) _____

☐ Out Patient

☐ Prenatal ☐ Multiphasic

☐ Diagnostic ☐ Other _____

☐ Employee _____ (Division) _____

Last Name _____ First _____ Middle _____

Ward _____ History or OPD # _____ Date Adm _____ Admission Diagnosis _____

Age _____ Sex ☐ M ☐ F Color ☐ W ☐ N Other—Specify _____ Marital Status ☐ S ☐ M ☐ W ☐ D ☐ LS

Nativity _____ Occupation _____

Film Nos _____ Technician _____

FINDINGSTuberculousTYPE OR DEGREE

- 1 ☐ Primary Infection
- 2 ☐ Minimal
- 3 ☐ Mod Adv
- 4 ☐ Far Adv
- 5 ☐ Pleural Effusion
- 6 ☐ Hematogenous
- 7 ☐ Silicotic Atelectasis

CLINICAL STATUS

- 1 ☐ Inactive
- 2 ☐ Active
- 3 ☐ Undetermined Activity

Non-Tuberculous

- 1 ☐ Pulmonary Disease (Tentative Diagnosis)
- 2 ☐ Pleural Disease
- 3 ☐ Abnormal Aorta
- 4 ☐ Abnormal Heart
- 5 ☐ Mediastinal Disease
- 6 ☐ Lung Anomaly
- 7 ☐ Rib Anomaly
- 8 ☐ Thoracic Cage Lesion
- 9 ☐ Lung Scars
- 10 ☐ Pleural Scars
- 11 ☐ Diaphragmatic Disease
- 12 ☐ Chest or Lung Injuries
- 13 ☐ Neoplasm
- 14 ☐ Others—Specify _____

CONCLUSIONS

- 1 ☐ NEGATIVE CHEST
- 2 ☐ ABNORMAL CHEST No further X-ray unless clinically indicated
- 3 ☐ ABNORMAL CHEST Further study recommended

FINAL DIAGNOSIS _____

M D

have chest x rays at the time of registration so that when they enter labor they are taken immediately to delivery rooms. On an average, about 85 per cent of the patients admitted to the hospital are examined by miniature roentgenography, the remaining 15 per cent being composed largely of emergency admissions. Chest x-rays are taken on a twenty-four hour schedule. The films are developed at the end of each day, excepting week ends and holidays and read the following morning.

The resident in pulmonary diseases begins the day's work by reading the films taken the previous day. A staff physician of the Pulmonary Division checks the resident's findings and reads, in addition, all films taken since his last reading. In the course of the week each film is read independently by at least two members of the visiting staff expert in roentgen interpretation of chest disease. An orientation sheet containing a concise notation of the roentgen findings is sent to the ward within twenty-four hours of the patient's admission. The upper half of the orientation sheet is filled out on admission; the lower half, after the final diagnosis is made. The sample of data to be presented shortly is based on the final diagnosis (Table 2).

Patients suspected of having pulmonary tuberculosis on the basis of the admission x-ray findings are immediately transferred to the tuberculosis wards. The condition of patients revealing nontuberculous diseases is brought to the attention of the physicians of the particular service involved; the members of the Pulmonary Division maintaining close contact with the patient and supervising the treatment until the final disposition. Follow-up is continued in the Chest Clinic. The direction and operation of the admission chest x-ray program at the Morrisania City Hospital is by physicians specializing in chest diseases. Institutions without a chest unit utilize a Tuberculosis Officer or some similar agents to integrate the several services.

As noted in the orientation sheet, three broad groupings are used in classifying the admission chest x-ray findings (Table 2). Group A includes instances in which no changes are seen in the miniature films of sufficient importance

to warrant reexamination by 14 x 17 mm films. This group includes malformations or developmental anomalies of the thoracic cage or of the lungs such as azygos lobes or cervical ribs, discrete calcified foci, pleural thickenings or obliteration of costophrenic sinuses as well as diffuse emphysematous changes or accentuated bronchovascular markings in older age groups. In questionable cases the film is over-read, proper consideration being given to the admission diagnosis.

Group B includes instances of cardiac enlargement and/or undue prominence of the large blood vessels. Patients with such abnormalities are referred to the Cardiovascular Division. If the cardiac enlargement is associated with gross disease in the lungs and/or pleura such as infarction, pneumonia or large pleural effusion the condition is classified in Group C. The latter includes all patients whose films show changes in the lungs and/or pleura of sufficient significance to warrant further study by 14 x 17 mm films and other diagnostic aids, if necessary. Since the installation of the photofluorographic unit at the Morrisania City Hospital approximately 1,200 chest cases, exclusive of 800 cardiac suspects, are found annually.

Of the first 20,000 consecutive admissions to the Morrisania City Hospital 2,644 or approximately 13 per cent revealed significant chest abnormalities (Table 3). An additional 8 per cent not included in Table 3, revealed cardiovascular abnormalities. In other words one of every five patients admitted to the Morrisania City Hos-

TABLE 3
CHEST ABNORMALITIES AMONG 20,000 CONSECUTIVE HOSPITAL ADMISSIONS DISCOVERED BY ROUTINE PHOTOFLUOROGRAPHY

Service	The Known on Admission	The Unknown on Admission	Non Tuberculous Pulmonary Disease
Medicine (including Chest Division)	369	744	1478
Surgery	16	39	140
Urology	10	27	69
Obstetrics and Gynecology	9	29	29
Prenatal	11	19	18
Other Services	15	38	114

420 2.15% 416 2.08% 1798 8.99%

pital has abnormal findings referable to the heart and/or lungs to which attention is drawn often for the first time, through the use of routine chest photoroentgenography. A follow-up study of the cardiac suspects was not made but there is reason to believe that in a sizable percentage the admission chest x ray was instrumental in directing attention to the possible existence of cardiac disease.

The experiences reported by Bitt and co-workers are worth citing. During 1953, photo fluorograms of all adult patients admitted to the Hospital of St Raphael, New Haven Conn were studied for cardiovascular disease. In addition to the routine P A film, a left lateral view was taken on all patients except the very obese and the prenatal group. Suspicious cardiovascular silhouettes were selected for further study. Of 6,439 adults 709 of whom were suspected of having cardiovascular abnormality, a follow up study of 595 revealed 497 (83 per cent) to have cardiovascular disease. One hundred and ninety-six (47 per cent) were unaware of the presence of such diseases. Admittedly the patients were of a selected group and of more advanced age than are encountered in usual surveys. Nevertheless the results are quite impressive.

Study of a group of 601 consecutive patients with tuberculosis during the first two years of the Morrisania City Hospital project showed that 288 or 28 per cent knew of their disease on admission the majority having been referred for emergency treatment and 313 or 52 per cent were unaware of their disease. On the basis of the total admissions to the Morrisania City Hospital, examined by routine chest roentgenography 2.08 per cent of the patients were found to have pulmonary tuberculosis for the first time, an incidence of more than 20 per thousand. It should be noted that in contrast to the group admitted with known tuberculosis, those with unknown disease included only 15 per cent with advanced and 60 per cent with minimal tuberculosis.

The clinical material at the Morrisania City Hospital comprises a select group of patients including large numbers of Negroes and Puerto Ricans in whom tuberculosis is much more preva-

lent and more virulent than in the general population. The recent decline in the incidence of tuberculosis in the population as a whole is probably being neutralized to some degree by the fact that in large urban centers, as in New York City, non-whites are now making up a larger percentage of the population. Obviously, a case finding study in a hospital located in a section of the city with a smaller percentage of Negroes and Puerto Ricans than in the Morrisania district would undoubtedly reveal a lesser incidence of tuberculosis. In any event, the incidence would be materially higher in routine hospital admissions than in the general population. The finding of more than twenty persons per thousand with clinically significant tuberculosis among routine admissions to the Morrisania City Hospital who were unaware of their disease is impressive. As mentioned previously, community surveys reveal an incidence of reportable or "probably" active tuberculosis of one to three per thousand.

From the very inception of the project at the Morrisania City Hospital particular attention was paid to the problem of pulmonary neoplasms. It was found that although a sizable number of unsuspected tumors are discovered in the course of routine chest photofluorography, the vast majority are in advanced stages and not amenable to surgical treatment. One of the reasons few cases of early carcinoma of the lung are discovered among general hospital admissions is because the majority of patients enter the institution with acute disease or acute episodes superimposed on chronic illnesses. In a patient with bronchiogenic carcinoma associated with symptoms, the disease is almost invariably too advanced to be benefited by surgery. However, one should not lose sight of the fact that benign intrathoracic neoplasms are also of serious import because of their location within the restricted confines of the chest cavity. Since surgery offers the most rewarding results in the treatment of benign intrathoracic neoplasms the discovery and removal of such tumors, as a result of routine chest photofluorography, are notable achievements in themselves.

In addition to its practical value as a case finding method, a photofluorographic machine in-

stalled in a hospital serves as an auxiliary to the department of roentgenology. The unit may be used for the examination of those seeking employment as well as in the routine examination of house physicians, nurses and other hospital personnel. The admission film is occasionally the sole means of demonstrating chest disease because once a patient is in the ward the rapid deterioration of his condition may prevent more thorough roentgenologic studies. The establishment of a photofluorographic unit in an institution makes physicians chest conscious by providing almost daily examples of what might have been missed had a chest x ray been omitted.

A chest x ray should be included as part of the preoperative preparation of every patient about to undergo surgery. Since patients are often operated on shortly after hospitalization this procedure is often omitted with catastrophic results in some cases. Patients with chronic pulmonary diseases such as pulmonary tuberculosis, bronchiectasis and neoplasms who are scheduled for operation on a later date should have chest x rays taken the day prior to operation to note any last minute developments. Occasionally one meets with unexpected changes in the chest x ray which may prompt postponement of the contemplated operation.

A request card for a chest x ray can be made part of the preop orders. The chest x ray is read the same day and any abnormal findings immediately relayed to the anesthesiologist and surgeon. Loder reported on the use of this technique in 1 000 consecutive surgical cases. In 116 cases abnormalities were found and in twenty nine of these operations were postponed or cancelled. This number included six newly discovered cases of pulmonary tuberculosis, three cases of carcinoma, two cases of severe pulmonary collapse and infection and a variety of other conditions. Significantly in three cases early in the series reports of the roentgen findings were received too late and operations were done. These patients developed postoperative complications.

ROUTINE CHEST X RAYS IN CLINICS

Increasing numbers of patients are having

chest x rays in our patient departments of general hospitals and in special clinics connected with various institutions. Unfortunately the number of clinics utilizing this valuable diagnostic aid as a routine measure is still small. Yet in some respects the early diagnosis of chest disease in clinic patients is even more pressing than in patients occupying hospital beds. Expeditious handling and segregation of patients in city hospital clinics is urgent. The examining rooms and corridors are apt to be filled with patients having minor ailments as well as those with major diseases including acute infections requiring immediate admission to the wards. Too much time is lost in most clinics before a chest x ray is taken which in a properly organized unit should be made of each patient on registration. The chest x ray should not be reserved for problem cases; one meets with more problem cases after chest x rays are taken.

The results of routine roentgenography of all prenatal registrants at the Morrisania City Hospital have demonstrated the value of this procedure. Of 2 400 consecutive prenatal registrants in a period of two years no less than 40 (1.7 per cent) were found to have clinically significant pulmonary tuberculosis, some with advanced disease. In twenty-two the disease was discovered for the first time by the routine employment of photofluorography. An additional thirty-one were found to have various nontuberculous conditions exclusive of cardiac diseases requiring further study. Interestingly enough a study made some years ago in the prenatal clinic of the same institution revealed one defect to every four patients but *not a single instance of pulmonary tuberculosis*. Needless to say routine roentgenography was not used at the time this particular study was made.

The experience at the Morrisania City Hospital with prenatal registrants has been duplicated in other institutions. Bickerstaff and co-workers found on routine photofluorographic examinations of 3 576 prenatal cases 43 or 1.2 per cent with tuberculosis or suspected tuberculosis, 25 or 0.7 per cent with cardiovascular disease and a number with other conditions. The unusually large percentage of Negroes and

Puerto Ricans among the Morrisania City Hospital prenatal registrants accounts for the high incidence of tuberculosis found in this hospital group. Bickerstaff and his co-workers draw attention to the important finding that a comparison of the group of patients whose tuberculosis was diagnosed prenatally with those whose disease was discovered for the first time postpartum showed a much more disastrous course of events in both mothers and infants in the latter group.

Convincing proof, if any additional evidence were needed, of the importance of routine chest roentgenography in the diagnosis of pleuropulmonary disease is available in chest clinics where patients are referred by physicians with the knowledge or strong suspicion that pulmonary disease is present. In 1950, N. Wynn Williams had roentgen examinations made of 228 consecutive patients diagnosed as having "pneumonia." These were routine referrals by physicians to his chest clinic. Twenty-seven patients suspected of having pneumonia but in whom the x-rays failed to reveal evidence of disease were excluded from the study. Those with abnormal chest x-rays were followed until a "normal" film was obtained or a definitive diagnosis established. In 156 the diagnosis of pneumonia was confirmed the disease resolving in the course of time. In nineteen a second pulmonary condition not related to the pneumonia, was discovered as a result of the roentgen examination. In forty, or about 20 per cent, the diagnosis was incorrect. Instead of pneumonia, the disease proved to be tuberculosis, pleural effusion, bronchiectasis, neoplasm, cardiac disease or some other cause. In brief, "pneumonia," a disease easily recognized by the average physician, when subjected to the light of roentgenography may turn out to be anything but pneumonia.

As indicated in the preceding pages, unsuspected chest disease is discovered occasionally in apparently healthy persons and much more often among hospital patients. It stands to reason,

therefore, that those seeking attention in physicians' offices probably occupy an intermediary position insofar as the incidence of discoverable chest disease is concerned. This presumption is borne out by the experience of physicians in chest clinics where patients suspected of having disease are referred by their private physicians. Southerland established a radiographic center for patients of general practitioners. Of all the physicians in the community, 280 or approximately 50 per cent availed themselves of the service. The patients were first screened by miniature films and, when necessary, large films were used. Those found to have significant abnormalities were referred to more specialized thoracic units. Of a total of 5,072 persons examined, 227 or approximately 4 per cent were found in need of more intensive investigation. The final diagnosis of the 227 included 154 with active pulmonary tuberculosis of whom 125 had acid fast bacilli in the sputum. Twenty had intrathoracic new growths and the remainder, a variety of non-tuberculous diseases.

The importance of Southerland's study lies in the fact that a center of this type bridges the gap between the general practitioner, who may not have adequate radiographic equipment readily available, and the thoracic unit in a regional hospital where problem cases can be studied more intensively by a team of physicians and surgeons expert in their respective fields. The radiographic center serves the additional purpose of enabling general practitioners to refer patients to a unit which is not designated specifically a tuberculosis clinic. Many patients fear the publicity associated with a visit to a tuberculosis clinic and the inevitable visit of a public health nurse should a "spot" be found in a lung. In a radiographic center, such as the one conducted by Southerland, a preliminary screening is immediately available. If an individual is found to have a suspicious lesion, it is usually not difficult to pursue the matter further.

Routine Chest X Rays and the Private Practitioner

It is estimated that approximately 16 to 18 million persons in this country consult physicians annually. The office of the private practitioner is

obviously an ideal place for finding chest diseases providing full use is made of the opportunities and adequate facilities are made available for

diagnosis. Unfortunately, promotional activities, incident to short term intensive case finding projects have concentrated their appeal to the selling of "free x-rays" to the masses. Comparatively little attention is directed to the unique position which the practitioner occupies in his relation to the sick person. The wealth of case finding material available in a general practitioner's office was strikingly demonstrated by one physician, Dr. A. C. Daniels, in his own practice in Marion County, California.

Dr. Daniels' report covered a short period from October, 1941 to April, 1942. During this time he fluoroscoped routinely 250 persons which included all new patients who passed through his office. In suspected disease 14 of 17 in films were taken. This procedure resulted in the discovery of seven cases of active pulmonary tuberculosis,

an incidence of 2.8 per cent. Only one patient had physical signs suggestive of the disease and another suspected that he might have tuberculosis. Comparing these results with his previous experience, Daniels noted that he had discovered five cases of active tuberculosis in the preceding seven years. On the basis of his findings, this investigator estimated that if the prevalence of 2.8 per cent of active cases discovered in his practice were applicable to that of other physicians in the same community, the 15,000 patients who consulted doctors would have revealed about 400 cases of active tuberculosis. The doctor's office represents a great natural sieve, operating day in and day out through which are channelled patients not only with tuberculosis but other chest diseases, many with abnormalities of a type to be discussed in the chapters to follow.

Bibliography

- ANDERSON R. J. Tuberculosis in Mental Hospitals. *Pub Health Rep* 64:1 1949.
- ASKEW J. B. Impact on the Department of Public Health of the San Diego Mass Chest X Ray Survey. *Pub Health Rep* 67:31 1952.
- BATT H. M., ALLEN J. M., TREDER F. H. and SHAPIRO R. Photofluorographic Detection of Cardiovascular Disease in a General Hospital. *New England J Med* 251:934 1954.
- BICKELSTAFF H. J., COVISTOCK G. W. and BURKE M. H. Routine Antenatal Chest X Ray Findings in Patients Drawn from a Currently Surveyed Population. *Am J Obst & Gynec* 61:41 1951.
- BRYANT J. Tuberculosis Case Finding in General Hospitals. *Pub Health Rep*, 65:710 1950.
- BUCHSBERG A., LUBLINER R. and RUBIN E. H. Carcinoma of the Lung: Duration of Life of Individuals Not Treated Surgically. *Dis Chest* 20:257 1951.
- CAMPBELL J. A., SIEGAL W. and WORTH H. E. Niagara Falls Mass Chest X Ray Survey. *New York State J Med* 49:2779 1949.
- CALLEY J. H. The Results of the Boston Chest X Ray Survey. *New England J Med* 243:631 1950.
- CHRISTIE A. C. Mass Screening Techniques for Chest Diseases. *JAMA* 151:114 1953.
- CHURCHILL A. S. Bronchogenic Carcinoma in San Diego County. *California Med* 78:232 1953.
- COTTON R. H. Importance of Modern Chest Examination. *Ann West Med & Surg*, 3:37 1949.
- COUNCIL ON MEDICAL SERVICE. Summary of a Study of Multiple Screening. *JAMA* 153:1047 1953.
- DANIELS A. C. Routine Chest Fluoroscopy in General Practice. Tuberculosis Supplement. *California & West Med*, 57:44 1953.
- DROLET G. J. Los Angeles County Wide Chest X Ray Survey of 1950. Tuberc Control Foundation. Los Angeles 1953.
- ELKINCH D. E., SCHILLER I. A., and EDWARDS H. R. Army X Ray Examination for Tuberculosis. *Am Rev Tuberc*, 47:113 1943.
- GARLAND I. H. The Detection of Carcinoma of the Lung by Screening Procedures. Particularly Photofluorography. *Am J Roentgenol* 74:401 1955.
- GOULD D. M. Nontuberculous Lesions Found in Mass X Ray Surveys. *JAMA* 127:753 1945.
- GOWEN G. H. and FRANK B. Screening for Chest Pathology Using Mass X Ray Survey Technique. *Ann Int Med* 36:138 1952.
- GUINN L. W. Mass Roentgenographic Screening As a Lung Cancer Control Measure. *Cancer*, 8:219 1955.
- G
- H June 9 1949 (letter).
- HODGES F. J. Fluorographic Examination of the Chest as Routine Hospital Procedure. *Radiology* 33:453 1942.
- HODGES F. J. Discussion of the Adult Silent Chest by G. M. Landan and H. A. Schorsch. *Radiology* 50:37 1948.
- HODGES F. J. X Ray Examinations of Admissions to General Hospitals. *Tr Nat Tuberc A*, 45th Annual Meeting 335 1949.
- KERLANDER A. B. and CARROLL B. E. Case Finding Through Multiple Screening. *Pub Health Rep*, 68:1035, 1953.
- LEES H. D. is in Medical Students and Nurses. *JAMA* 153:1047 1953.
- LOOPER R. Preoperative Chest Radiography. *Lancet*, 1:1150 1953.
- Analysis:

CHEST ROENTGENOGRAPHY IN MASS SURVEYS

17

- McNULTY J W Clinical Follow Up Study of 398 Patients Suspected of Having Lung Cancer Discovered in the Boston Chest X Ray Survey *New England J Med* 210 14 1954
- Morse D G The Chest X Ray *Dis Chest* 10 515 1944
- OATWAY W H Jr The Current Status of Routine Chest X Raying in General Hospitals of the United States September 1948 *J Arizona M A*, 6 73 1949
- OSCHLER W R Tuberculosis Control Program of Nine California Mental Institutions *Pub Health Rep* 64 4 1949
- PALCHAMIS W T Prevalence of Previously Unknown Tuberculosis in Persons Not Participating in Mass Chest Roentgenographic Surveys *Am Rev Tuberc*, 65 451 1952
- PAVLOVA P A Community Wide Chest X Ray Survey in The Medical Profession *Pub Health Rep* 66 1596 1951
- PINNEY M *Pulmonary Tuberculosis in the Adult* Springfield Illinois: Charles C Thomas Publisher 1945
- PORTER D E The Importance of the Hospital As a Tuberculosis Case Finding Center Hospital Council of Greater New York and New York Tuberculosis and Health A 1950
- REISNER D and RIKLI A Community Wide Chest X Ray Survey IV Diagnostic Clinic *Pub Health Rep* 66 473 1951
- ROEMERICH W WEBER F J HILL, F J., and AMOS L Preliminary Report on a Community Wide Chest X Ray Survey *Pub Health Rep* 66 1285 1948
- REISTER D D WILLIAMSON C R., and MOORE F E Heart Disease Case Finding by Means of 70 Millimeter Photofluorographic Films *Circulation* 4 641 1951
- SCILCA M H and AMES, W R Methods of Tuberculosis Case-Finding in the Community *Mass Chest X Ray Survey A Summary of Follow Up Findings in 200 000 Persons Examined in Erie County New York New York State J Med* 49 2775 1949
- SIDPMAN S J Editorial Case Finding *Am Rev Tuberc*, 56 606 1947
- SIEGAL W., WIRTH H E and CAMPBELL J A Niagara Falls Mass Chest X Ray Survey *New York State J Med*, 49 7783 1949
- SWINTI V and RLAIN, E H Routine Chest X Rays Supporting Evidence *Hospital* 23 45 1949
- SOUTHERLAND H Mass Radiography and Pulmonary Tuberculosis in General Practice *Lancet* 1 152 1952
- WILLIAMS N X Ray Examination in Pneumonia *Brit M J* 1 179 1950

Diseases of Metabolism

Introduction

THE METABOLIC diseases which may affect the lungs are usually encountered in infancy and early childhood. Those appearing later in life may occasionally be traced to an earlier age but in many instances this is not possible because developmental adjustments during growth tend to obscure the underlying defect. Recurrent respiratory infections are also apt to becloud the nature of the original disease. However, there is reason to suspect that certain cases of cystic lungs, diffuse interstitial pulmonary fibrosis, atypical forms of bronchiectasis and several other conditions to be described later, discovered for the first time in adults, represent late manifestations of disease either developmental in origin or which appeared shortly after birth.

The reason why comparatively few metabolic disorders with pulmonary involvement are encountered in adulthood is due to the fact that children with major metabolic derangements sel-

dom reach maturity. With greater awareness of the nature of some of the metabolic diseases and the widespread use of antibacterial agents to combat infection, more children are now reaching adulthood. This is attested by the increasing number of cases currently being reported of metabolic diseases with pulmonary involvement in older age groups.

Metabolic diseases may affect the lungs through structural damage of the organs and by providing conditions favoring infection. The latter is an almost inevitable accompaniment of several of the disturbances to be discussed. In view of the profound alterations which take place in the vascular and internal secretory organs, as well as in the reticuloendothelial system, it may be pertinent to dilate on certain aspects of the problem which have an important, although indirect, bearing on the major topic of the discussion.

Hypertrophic Pulmonary Osteoarthropathy

As described originally by Bamberger, and amplified by Marie, hypertrophic pulmonary osteoarthropathy is a symmetrical osteitis of the four limbs chiefly localized to the phalangeal and terminal epiphyses of the long bones of the forearm and leg, sometimes extending to the roots of the limb and flat bones and accompanied by a dorsal kyphosis and some affection of the joints. The original description of the condition is therefore, more inclusive than simple clubbing of fingers and toes. According to Hansen, clubbing and osteoarthropathy are similar reactions. They may be independent of each other or one may precede the other. Finger clubbing is more apt to occur in association with bronchiectasis

and diffuse pulmonary disease, the condition developing and disappearing rather slowly. Periosteal proliferation is more likely to be associated with carcinoma and localized pulmonary disease, the condition developing and disappearing more rapidly.

As far back as antiquity, physicians have speculated on the possible relationship between digital clubbing and various diseases. At first, clubbing was noted in association with chronic diseases, notably pulmonary tuberculosis, bronchiectasis, lung abscess, empyema and congenital heart disease. Later a considerable number of other conditions were found to be accompanied with finger clubbing. A congenital form, with-

our changes in long bones is also recognized. A partial list of diseases in addition to those mentioned which may be associated with hypertrophic pulmonary osteoarthropathy includes carcinoma of the nasopharynx and thymus malignant lung and pleural tumors myelogenous leukemia chronic valvular heart disease cirrhosis of the liver ulcerative colitis chronic pyloric obstruction sprue pulmonary and peripheral arteriovenous aneurysms Wiernan and co-workers analyzed the occurrence of articular manifestations in 1074 cases in which resection was done for major pulmonary diseases. As shown in Table 4 the highest incidence is re-

after subtotal thyroidectomy for exophthalmic goiter. Signs of osteoarthropathy appeared coincidentally with symptoms of postoperative hypothyroidism. After the institution of thyroid treatment there was noted a thinning of the subperiosteal bone as well as clinical improvement.

In 1915 Locke drew attention to the fact that acromegaly is so closely related to hypertrophic pulmonary osteoarthropathy that in some of the cases reported in the literature patients with acromegaly had been included among those considered to have pulmonary osteoarthropathy. In one instance of primary carcinoma of the lung the patient was found to have hyperplasia of the pituitary chromophil cells. Fried reported four cases of bronchiogenic carcinoma associated with advanced degrees of pulmonary osteoarthropathy. In his cases also the presence of acromegaly was attested by characteristic facies tufting of the terminal phalanges of the fingers and toes hirsutism macroglossia and thickening of the cranial vault. Fried concluded that diffuse osteoarthropathy found in neoplastic diseases of the lungs is due to an endocrine imbalance all in to acromegaly.

Ray and Fisher noted that osteoarthropathy is much more often associated with peripherally situated malignant neoplasms than with main bronchial tumors. In rapidly developing osteoarthropathy associated with bronchiogenic carcinoma there may occur a painful arthritis at times also peripheral neuritis. Ellman encountered six cases in a group of 200 consecutive bronchial carcinomas who presented joint manifestations in the form of acute or chronic polyarthritis as the initial complaint. In none was there any real evidence of extensive tissue breakdown or appreciable infection to account for the joint symptoms. Semple and McCluskie studied twenty four patients who had joint symptoms in association with lung cancer. They showed clinical and roentgenological evidence of hypertrophic pulmonary osteoarthropathy. In thirteen patients who survived tumor resection they noted increased joint mobility often within hours of the operation. Patients who had been

TABLE 4
RELATIVE INCIDENCE OF PULMONARY OSTEOARTHROPATHY AS SEEN IN PLEUROPLEURAL RESECTIONS

Specific Lesions	Resected	Articular pathology Present	Incidence %
Pleural mesothelioma	14	8	57.1
Bronchectasis	189	18	9.5
Lung Abscess	34	6	17.6
Cyst	30	3	10.0
Malignant tumor	481	5	0.6
Tuberculosis	157	1	0
Miscellaneous benign tumors and granulomas etc	119	0	0
Total	1044	61	60
From Wiernan 1460 and Clagett and McDonald 1954		155	

ported in pleural mesotheliomas lung abscess and cysts. Harper and Patterson draw attention to the fact that occasionally pulmonary osteoarthropathy may precede classic symptoms and signs of carcinoma of the lung. They found reports of forty seven cases in which the interval ranged from two to thirty six months.

Various explanations have been offered for the development of hypertrophic pulmonary osteoarthropathy. These include anoxic infectious neurotic toxic and endocrine factors. There is in direct evidence that in some cases the condition is related to an endocrine imbalance. This hypothesis finds support in a number of reported instances of osteoarthropathy occurring in patients with thyroid disease a condition in which the pituitary gland plays a vital role. Thomas and others reported cases of osteoarthropathy occurring

bedridden with 'arthritis' for weeks or months were walking normally within a few days

The mechanisms involved in the development of osteoarthropathy are not clearly understood. They are certainly too complex to be resolved by a single formula. The presence of symptoms of rheumatoid arthritis especially if the latter is associated with acromegalic features and finger-clubbing, should direct attention to the possible presence of a bronchiogenic carcinoma. Chest x rays should be taken in various projections to make certain that a small neoplasm is not lurking behind the heart or is hidden in some other recess of the thoracic cage (Figure 1). Ellman suspects that the reason for the dramatic response of the joint swellings to lung resection for carcinoma might be in factors intrinsic in the lung itself. Vogl and co workers suspect that an abnormally increased peripheral blood flow plays a role in the pathogenesis of pulmonary osteoarthropathy. The derangement of the circulation may be de-

pendent upon an abnormal intrathoracic reflex which is promptly abolished by surgical removal of the affected lobe. Flavell obtained marked symptomatic improvement of the osteoarthropathy, in irremovable bronchial carcinoma, by severing the vagus nerve alone on the affected side. This points to a neural reflex as one of the mechanisms involved.

Bloom documented a case in which metastatic lesions from a primary carcinoma of the lung were found in the pituitary gland. There was hypertrophic pulmonary osteoarthropathy associated with acromegalic features. A report by Peabody draws attention to the occasional association of bronchiogenic carcinoma and diabetes insipidus. In six cases the evidence strongly favored the assumption that the latter was a manifestation of metastases involving the posterior lobe of the pituitary gland. In an additional six cases, culled from the literature, the diabetes insipidus was found to be caused by metastases in

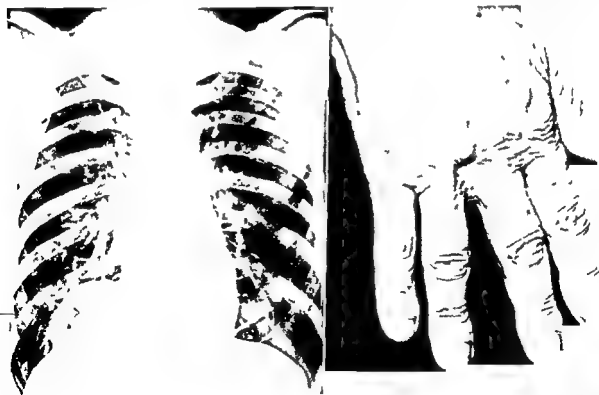


Figure 1
density
spine)

||||| || |||

- of fingers. A (Left) Round well circumscribed mass to be situated posteriorly adjacent to the spine. A peripheral tumor was found histologically (carcinoma)

the posterior portion of the pituitary neural unit. In each instance the primary disease was a bronchiogenic carcinoma.

These observations may find a common denominator in the action of the pituitary gland on the vascular and hemopoietic systems. In a study of the interrelationship between the lungs and the pituitary gland Wochling concluded that diseases of the lungs, such as cancer (primary and metastatic), chronic pulmonary suppuration and pulmonary osteoarthropathy are often associated with pituitary chromophil hyperplasia. This author suggests that lung diseases produce an inflammatory reaction which calls for vascularization, oxygenation and hemopoiesis and this process in turn results in a compensatory hyperplasia of the pituitary chromophil cells. It is noteworthy that animal experiments have shown a close relationship between the pituitary gland and the development of tumors. Removal of the pituitary suppresses the growth of cancer. The current use of hormonal treatment of malignant disease of the prostate and breast with stilbesterol and testosterone, respectively, is essentially a form of 'medical hypophysectomy'. As for the direct agents involved in the production of digital clubbing it is generally believed that the latter is due to hypertrophy and hyperplasia of tissues caused by increased blood flow and nutrition of the affected parts resulting in minute arteriovenous anastomoses. Charr and Swenson demonstrated, by means of infra-red photographs of living persons and also postmortem arteriograms, that the local vascular bed is increased and widened in cases of clubbing. This is assumed to indicate an increased peripheral blood flow. An accompanying low tissue oxygen tension may be a contributing factor. This mechanism can also be demonstrated in unilateral digital clubbing associated with arteriovenous fistula. In two cases of unilateral clubbing, one following trauma of the right limb and the other congenital in origin, Wilson found an excess of blood flow of the affected parts. As was mentioned previously, the successful treatment of pulmonary lesions associated with joint pains and clubbing may lead to a return of the fingers to a more normal appearance. In most instances, the disappearance of clubbing after operation is more apparent than real. There are few objective studies on record documenting such transformations.

Diabetes and Pulmonary Infections

PHYSIOLOGICAL CONSIDERATIONS

Diabetes favors infection of the lungs as it does of the skin, kidneys and other parts of the body. The reason for the vulnerability of the diabetic to infection is not entirely clear. For a time it was believed that the increased sugar content of the blood provides a medium favoring the growth of microorganisms. As is well known, the addition of glucose to culture media enhances the growth of the tubercle bacillus, yet, pyogenic organisms do not grow better in vitro in a blood sugar medium than in a blood medium alone. But if the blood is obtained from a patient in a diabetic coma certain bacteria do grow better. More weight is ascribed to faulty metabolism of the tissues. Dogs rendered diabetic by pancreatectomy show a greater degree of inflammatory necrosis of the skin than do the controls (Horster). Likewise, depancreatized

dogs show increased susceptibility to infection with the tubercle bacillus (Steinbach and others). The predisposition of patients with prolonged pancreatic insufficiency to infection is strikingly demonstrated in the massive necrotizing pneumonias encountered in patients with pancreatic lithiasis (Moolten). Similar factors may be at play in infants and children with pulmonary infections associated with cystic fibrosis of the pancreas to be described shortly.

The aforementioned studies would indicate that the susceptibility of the diabetic to infection is due in part to faulty carbohydrate metabolism caused by absence of islet-cell secretion (insulin). In addition, there may be unexplained weaknesses within the lung structure itself. Root and Bloor made chemical analyses of lungs removed at autopsy from diabetes. They found strikingly lower concentrations of phospholipid

and lipid than in nondiabetic patients. Additional factors which may favor pulmonary infections in the diabetic are vitamin A and C deficiencies, endocrine disturbances and lowered local resistance due to vascular damage of tissues.

Infection is particularly serious in the uncontrolled diabetic because of the associated starvation, dehydration and other conditions resulting in ketosis. Dubos found that infection in the diabetic is facilitated during ketosis by the additive effect of two factors: (1) the presence of ketone bodies in abnormally high concentrations, and (2) the decreased production of lactic acid at the site of inflammation. Lactic acid inhibits and ketone bodies stimulate the multiplication of staphylococci and tubercle bacilli at the acid reactions which usually prevail in inflammatory areas. This may explain in part the susceptibility to infection which is often associated with ketosis of various etiology.

DIABETES AND PULMONARY TUBERCULOSIS

The diabetic is particularly vulnerable to the development of tuberculosis which is apt to be in an advanced stage and acutely progressive when first discovered. A survey conducted in Philadelphia begun in December 1945 and concluded in 1947 revealed twice as much tuberculosis in diabetics as in a comparable group of nondiabetics and three times as much *active* tuberculosis. A direct correlation could be shown between the increasing severity of diabetes and the increasing prevalence of active tuberculosis. These findings substantiate what has long been known regarding the two diseases. Previous estimates of the prevalence of tuberculosis in diabetics had been somewhat higher but clear cut distinctions had not always been made between active and inactive disease. The lower figures in the Philadelphia survey reflect also the considerable decline in the incidence of tuberculosis in recent years. The death rate from diabetes had shown relatively little change during the same period.

Recently published statistics from the Joslin Clinic are particularly significant. They reveal that early in the present century tuberculosis accounted for approximately 3 per cent of the

deaths among the diabetics in the Joslin Clinic between 1950 and 1952; the percentage fell to 0.9 per cent. In the population at large during the same period the incidence of deaths due to tuberculosis among diabetics was considerably higher. But in spite of the improved picture tuberculosis still remains one of the most serious complications encountered in diabetes particularly in uncontrolled diabetes.

The following data which I gathered at the Montefiore Hospital some years ago is in basic agreement with the reports cited. In a study of seventy-two elderly tuberculous diabetics the diabetes usually preceded the appearance of symptoms of tuberculosis. But there was reason to believe that in many instances probably the majority a latent tuberculous focus had been present prior to the diabetes. After the development of the diabetes an acute exacerbation of the latent tuberculosis took place. Occasionally one obtained a clear cut history of active tuberculosis brought to arrest and after the development of diabetes the occurrence of a relapse. At the present time with better means of controlling tuberculosis increasing numbers of individuals reach the diabetic age thereby affording greater opportunities for later reactivation of their tuberculosis. Since the introduction of isoniazid in the treatment of tuberculosis I have encountered a number of patients in whom there was reason to suspect that possibly the medication itself may have been instrumental in reducing the sugar tolerance in susceptible individuals to a point where frank diabetes appeared. This problem requires further study.

Much has been written of so called diabetic phthisis which is featured by a relative paucity of physical signs in contrast to the extensive caseation necrosis of lung tissue, a predilection of the disease for mid zonal and basal regions, a comparatively slight pleural reaction, a low incidence of extrapulmonary tuberculosis and a greater tendency to pulmonary hemorrhage. In older individuals in whom one expects to see a predominantly fibrotic tuberculosis unusual manifestations of the disease such as those mentioned are apt to be particularly impressive. These and other features of diabetic phthisis

may be related with the manner of onset and spread of the tuberculous process, the adequacy of the diabetic control as well as the age groups involved. Reactivation of a tuberculous process in a middle-aged person is apt to be from a subapical and parahilar focus, often initiated by ulceration of a caseocalcious lymph node into a regional bronchus. Excessive amounts of liquid sputum and recurring hemoptyses favor spread of the disease to the lower lobes. In an uncontrolled diabetic who had lost considerable weight and is possibly in acidosis, the resulting aspiration infection is all the more serious. However, in the majority of tuberculous diabetics, especially those encountered in general surveys and in private practice, one meets with inactive tuberculous foci in the upper lobes and so-called, "diabetic phthisis" of the type previously described is the exception. Nevertheless, tuberculosis in an elderly individual, in whatever form the lung disease takes, should bring to mind the possibility of a latent diabetes and the patient examined for the presence of excess sugar in the blood and urine.

It is not within the scope of this discussion to enter into the treatment of the tuberculous diabetic. Suffice it to mention that with the availability of potent antimicrobial agents the tuberculous diabetic has now an excellent chance of having his disease brought under control. Pneumothorax has been practically abandoned in the tuberculous diabetic, in fact, pneumothorax is rarely indicated even in the nondiabetic. Because of the unusual severity of the tuberculous process it is advisable to utilize the most potent anti-tuberculosis agents available as soon as the diagnosis of active tuberculosis is made, including streptomycin, para-aminosalicylic acid (PAS) and isoniazid. Since elderly individuals are apt to be intolerant to PAS, one uses preferably a combination of streptomycin and isoniazid. The underweight diabetic needs a high caloric diet, rich in carbohydrates and low in fat. Insulin is necessary to cover the excess of caloric intake. Occasionally, especially in the younger age groups, resection finds indications. In the management of the diabetic it is incumbent on the physician to take periodic x-rays of the chest in

order to discover tuberculosis in its earliest and most curable stages.

DIABETES AND NONTUBERCULOUS PULMONARY INFECTIONS

Although there are no reliable statistics of the incidence of nontuberculous pulmonary infections in diabetics, as compared to nondiabetics, experience teaches that acute pneumonias, pulmonary suppurations, fungous as well as spirochetal infections, when they occur in the uncontrolled diabetic, are apt to be especially severe and take on massive proportions. Suppurative pneumonia, almost invariably associated with abscess formation, is frequently encountered in the diabetic "Diabetic gangrene of the lung" and "diabetic pneumomalacia," well known to previous generations of physicians, are pungent descriptions of the condition (Figure 2).

Suppurative pneumonias and lung abscesses find fertile soil in the diabetic with poor mouth hygiene, pyorrhea and carious teeth, especially if the cough reflex and cleansing mechanism of the upper air passage are interfered with or suppressed, thereby allowing ingress of bacteria into the deeper recesses of the lungs. In the exceptional case there may be pulmonary abscesses caused by hematogenous implantations of infected emboli from distant foci (see Chapter 10). In many instances, aspiration infections follow operative procedures in the oral cavity or in other parts of the body under general anesthesia. Temporary loss of consciousness during coma or alcoholism or after deep sedation and shock treatment, are additional causes. Preexisting pneumonitis, bronchial asthma and advanced age are contributing elements. Of prime importance is the condition of the vascular bed. The presence of considerable degrees of atherosclerotic and occlusive endarteritic changes of the blood vessels favors massive pulmonary necrosis. Tuttle and Nicoll found that ligation of the pulmonary artery in the dog had a markedly deleterious effect on a beginning lung abscess, increasing the extent of involvement, limiting pyogenic membrane formation and sometimes causing gangrene of a lobe.

In some patients the disease is characterized by

fetid sputum indicative of an infection with a multiplicity of microorganisms including spirochetes and other anaerobic bacteria. In others, the disease is associated with nonfetid sputum. Smith found that although single strains of anaerobic organisms do not produce disease, when present in combination they act in symbiosis and produce gas, fetid odor and greenish pus. It may be difficult to determine whether or not the suppuration is of the, so called putrid or non putrid variety since one may merge into the other. Under the effects of antibacterial medication sputum elimination is quickly suppressed and loses its offensive odor. The particularly bad prognosis at one time associated with suppurative pneumonia and lung abscess in the diabetic has lost much of its grave import since the introduction of penicillin and other antibacterial agents. But the combination is still a serious challenge.

After institution of antibacterial medication and bronchoscopy to help cleanse the air passages also postural and supportive measures,

the disease clears in a few weeks, occasionally months. Surgery at the present time has relatively few indications. Resection finds a place in the treatment of chronic lung abscesses which fail to resolve under medical treatment or a persisting focus which may have mediated the acute exacerbation of the disease. But it should be emphasized that the mere amelioration of symptoms and apparent clearing of a lung abscess does not necessarily indicate eradication of the disease. Under the effects of penicillin the massive area of necrosis rapidly diminishes in size but a ring shadow may persist and at times be hardly discernible in the chest x-ray. The annular shadow represents a thin walled cavity, possibly associated with obstruction of the draining bronchus. Before an abscess can be considered healed sectional radiography is essential. Incidentally, similar 'ring' shadows are also being encountered with some frequency in pulmonary tuberculosis treated with antituberculosis agents, especially isoniazid. The excised specimen shows a smooth



Figure 2 Suppurative pneumonia in a diabetic. A (Left) the right lung scattered areas of high density with residual thickening of interlobar fissures.

consolidation in (Right) with

arrow of

glistening lining and in many instances no evidence of tuberculous granulation tissue can be demonstrated

The roentgen features of nontuberculous pulmonary infections in the diabetic differ little from those found in the nondiabetic excepting for the greater tendency in the former to cavity formation. In acute disease the affected lung may show multiple fluid levels indicative of rapid breakdown of tissues. It might be mentioned

that in general the presence of fluid levels in multiple cavities is more in keeping with non-tuberculous rather than tuberculous infection. The diagnosis depends on the presence or absence of acid fast bacilli in the sputum. A giant cavity may occupy the major portion of a lung simulating a pyopneumothorax. The latter may coexist as a result of rupture of an abscess into the pleural cavity.

Cystic Fibrosis of the Pancreas and Pulmonary Infections

INTRODUCTION

Fibrocystic disease of the pancreas has been a popular subject of discussion in pediatric literature since 1938 when Dorothy Andersen also Blackfan and May drew attention of physicians to the condition. Cystic fibrosis of the pancreas when it occurs is a hereditary disease and follows recessive Mendelian characteristics. The disease is an important cause of death in infancy and early childhood and is found in some statistics in as high as five per cent of autopsies of the young. With increasing awareness of the possible existence of cystic fibrosis of the pancreas the condition is now being recognized also in older children. Pugsley and Spence reported the case of a seventeen year old boy with cystic fibrosis of the pancreas associated with chronic pulmonary disease and cirrhosis of the liver. Among 335 cases studied di Sant Agnese included one nineteen years old.

ETIOLOGY

Based on studies by Blackfan and Wolbach also Farber and others it has long been known that fibrocystic disease of the pancreas is part of a generalized disease. Farber coined the term mucoviscidosis to describe this constitutional inadequacy which manifests itself in an abnormal secretory mechanism involving mucous glands. The obstruction of gland ducts by viscid mucus leads to atrophy and fibrosis of the organ. According to di Sant Agnese the condition involves perhaps all exocrine glands chiefly those of the pancreas, lungs, liver, sweat and salivary glands

This investigator believes that in the young this disorder accounts for virtually all cases of pancreatic deficiency for a majority of those with chronic (nontuberculous) lung disease and for one third of children with cirrhosis of the liver and portal hypertension. Noteworthy is the fact that abnormal sweat electrolyte concentration may lead to massive salt depletion and death.

In support of the generalized nature of mucoviscidosis Zuelzer and Newton found that of twenty eight children with cystic fibrosis of the pancreas examined at autopsy 85 per cent had changes in the gastrointestinal tract consisting of dilatation of glandular structures with mucus and atrophic flattening of the lining cells. Next in frequency were changes in the biliary passages which were noted in 60 per cent of the cases. The gallbladder of those affected were small, shrunken, gray in color with thickened walls and an almost solid opaque stringy colorless mucus filling the lumen. In keeping with this theory the pathologic process in the respiratory tract is assumed to be analogous to that in the pancreas and in other glandular organs. When pancreatic insufficiency is caused by a lesion which is local in character no pulmonary changes are found. When the pancreatic insufficiency is part of a generalized disease the lungs are usually involved and in a characteristic manner as will be described presently.

When cystic fibrosis of the pancreas was first recognized many were of the opinion that nutritional factors were primarily or largely responsible for the pulmonary changes. Andersen and her associates believed that as a result of

nutritional insufficiency and failure of the infant to absorb sufficient amounts of vitamin A, the respiratory epithelium becomes susceptible to infection and this results in suppuration, fibrosis, bronchiectasis and other changes. Current thought is that nutritional deficiencies play a secondary, though clinically important, role in the evolution of the pulmonary changes. Although squamous metaplasia of respiratory epithelium can be produced by vitamin A deficiency, a causal relationship cannot be established because metaplasia is not a constant feature and is not found in the absence of infection. Zuelzer and Newton point out that metaplasia of epithelium may occur in association with chronic inflammatory lesions in patients with normal pancreatic function whose intake and absorption of vitamin A are presumably adequate. Furthermore the administration of vitamin A does not improve significantly the pulmonary disease.

CLINICAL FEATURES

Fibrocystic disease of the pancreas presents a clinical picture not unlike that seen in celiac disease. As in the latter, the infant shows wasting, abdominal distention and eliminates bulky, fatty, foul-smelling stools. But in contrast to celiac disease, for which no cause has been found, fully developed fibrocystic disease of the pancreas reveals histological changes of the organ consisting of dilated acini, the ducts containing variable amounts of conglutinated mucinous substance. There is diffuse connective tissue formation in the gland but no actual inflammatory reaction and the islets of Langerhans are spared. Dietetic treatment is of little avail and the infant succumbs in a few months, or at most, a few years usually of a superimposed pulmonary infection.

It would take us too far afield to discuss the laboratory diagnosis of the disease except to point out that among the more important tests are the examination of the duodenal contents for lipase, amylase, and trypsin which are markedly decreased or absent in pancreatic fibrosis. The proteolytic power of the tested A piece of gelatine film (unfixed) is placed in a mixture of stool and tube and incubated in a test pe-

thirty minutes. If the stool is positive for trypsin the gelatine of the film is digested and shows clearing. False positive tests can be obtained. Hirsch and co-workers devised a pancreatic function test by measuring the postprandial rise in esterified fatty acids of the blood. Healthy children show an increase of such acids between thirty two and more than 200 per cent after test meals. In contrast, children with fibrocystic disease of the pancreas show slight, if any, postprandial increase. This indicates a failure of fat absorption from the bowel and reflects a disturbance of pancreatic function. Excessive fat in the stools is examined by the Sudan stain. In addition to the aforementioned, one obtains low cholesterol values and low vitamin A values as a result of poor absorption of fat.

A test which promises to be of considerable value, as a screen in the detection of fibrocystic disease of the pancreas, has been recently introduced by Silverman and Shirley. The test depends upon the fact that iodized fat (lipiodol) is digested and absorbed by normal children and the iodine is subsequently excreted in the urine in high concentration. In contrast, children with fibrocystic disease of the pancreas, whose digestion of fat is impaired, have a diminished urinary output of iodine. The test is quantitative as well as qualitative. The "sweat" test is becoming an important means of diagnosing fibrocystic disease of the pancreas. Studies carried out at the Babies Hospital, New York, have shown that children with this disease consistently exhibit a specific abnormality of sweat electrolytes. Sweat chloride and sodium are increased two to four times above the concentration found in controls. Of particular interest is the fact that in some of the apparently healthy relatives of the patients a sweat electrolyte pattern was found characteristic of the disease.

According to Andersen and others who have studied 100 cases, children with fibrocystic disease of the pancreas fall into one of three groups: (1) a neonatal group in which within the first week or two of life accumulation of nonliquefied meconium leads to failure of the pancreas to function. This is the

region of the ileocecal valve with resulting proximal dilatation of the gut and death. (2) A group in which death occurs between the neonatal period and six months of age from respiratory tract infections, although failure to gain weight and other evidence of the celiac syndrome may also be present, and (3) a group which survives longer than six months in which the initial symptoms are chiefly abdominal but symptoms referable to the respiratory tract soon become increasingly more pronounced eventually leading to a fatal issue. Of special interest from the viewpoint of the present discussion is the fact that fibrocystic disease of the pancreas is usually associated with pulmonary infection. In almost all 325 patients di Sant Agnese found pulmonary involvement of varying degree at some time in the course of the illness. The respiratory disease was severe and accounted for over 90 per cent of the 145 deaths.

PATHOLOGICAL FEATURES

The changes in the lungs are due primarily to obstruction of bronchi by viscid secretion which involve large as well as small channels. If a major bronchus is involved it may lead to atelectasis of an entire lobe or several lobes. Involvement of small bronchi leads to variable degrees of focal atelectasis and/or emphysema depending on the degree and extent of bronchial implication. Sooner or later infection supervenes especially with hemolytic staphylococci leading to suppurative bronchitis and bronchopneumonia. In long standing disease there is recurring pulmonary infection, fibrosis, bronchiectasis and emphysema.

The pulmonary involvement is associated with progressive respiratory insufficiency leading to cor pulmonale if the child lives long enough. Physiologic studies of pulmonary function in older children reported by West and co-workers have shown a pattern of dysfunction which these investigators believe is characteristic of the disease but which is subject to considerable variation in severity. They found both ventilatory insufficiency leading to dyspnea and disturbances in gas exchange leading to arterial hypoxia and carbon dioxide retention. The pulmonary dys-

function is ascribed chiefly to the factor of obstruction of bronchi by secretions causing ventilatory impediment, also an uneven distribution of tidal air.

ROENTGENOLOGY

The roentgen findings reveal the various pathologic changes mentioned. Early in the disease the bronchitic symptoms may not find expression in gross roentgen abnormalities but after repeated infections the presence of disease is revealed in accentuated perivascular and peribronchial markings located chiefly in the inner and midportions of both lungs. In a study of 211 children with cystic fibrosis of the pancreas di Sant Agnese found that in approximately 10 per cent the chest x-ray revealed massive atelectasis involving one or more lobes during the first episode of pulmonary involvement. The right lung was found especially vulnerable, in fact, not a single instance of left sided atelectasis was encountered. In advanced disease one finds patchy densities alternating with areas of highlight in keeping with the progressive consolidation, emphysema and bronchiectasis. Occasionally, the roentgen findings are sufficiently distinctive to suggest the nature of the underlying disease if the latter is not already known.

Keats draws attention to the fact that pulmonary emphysema may be one of the earliest roentgenologic signs of cystic fibrosis of the pancreas. The emphysema is usually irregular in distribution but may involve both lungs diffusely and to a marked degree. The emphysematous stage is transient and soon gives way to atelectasis and signs of infection.

Case 1 Female—Age Infant

Had repeated respiratory infections, shortness of breath and rattling in the chest since shortly after birth. At the age of seven months the infant was hospitalized because of inability to gain weight, malodorous bulky stools, fever, cough and vomiting. A diagnosis of cystic fibrosis of the pancreas was made. Chest x-rays revealed exaggerated bronchovascular markings and linear infiltrations involving chiefly the left upper lobe.

After a five-month period of improvement under antibiotics the infant was readmitted to the

hospital because of aggravation of symptoms. The chest x-ray now revealed patchy and linear infiltrations in the right lung as well as progressive changes in the left (Figure 3). Further tests confirmed the presence of cystic fibrosis of the pancreas. The infant was treated with various antibiotics and for a time gained weight but soon sustained a relapse, developed acute respiratory symptoms and died at the age of twenty six months. Autopsy revealed diffuse fibrosis and bronchiectasis with areas of bronchopneumonia in both lungs, also cystic fibrosis of the pancreas.

Krabbenhoft and Evans have drawn attention to the fact that infants with intracardiac septal defects may show pulmonary changes similar to those seen in cystic fibrosis of the pancreas. As in the latter the authors found variable degrees of pulmonary atelectasis and/or emphysema. Although infants with congenital heart disease do not exhibit abnormally viscid mucus of the degree encountered in mucoviscidosis, excessive amounts of mucus were observed in several of the cases. In considering these findings along with other pulmonary manifestations of infection the authors believe that serious thought should be given to both conditions in differential diagnosis.

The scope of this book does not permit the

inclusion of details of treatment. But, it might be mentioned that in addition to dietary measures including high protein, high caloric and slightly reduced fat intake, also large doses of vitamin, especially A and D, and pancreatic replacement, the greatest advances of recent years have been in the field of prevention and treatment of pulmonary infection through the use of antibacterial agents. Frequent sensitivity tests of the microorganisms obtained from the upper air passages and sputum are necessary to make certain that the particular antibiotic or combination of antibiotics is effective.

Stoppelman and Schwachman reported observations on 140 patients with mucoviscidosis treated with antibiotics at the Children's Medical Center, Boston, Mass., for periods as long as six years. Children with mild pulmonary involvement received continuously chlortetracycline or oxytetracycline alone, in average doses of less than 20 mg. daily per kilogram of body weight. Patients with moderate to extensive pulmonary involvement received a combination of agents such as sulfadiazine, chloramphenicol, or erythromycin in addition to chlortetracycline or oxytetracycline. Those with extensive pulmonary involvement were usually given penicillin or streptomycin aerosol therapy in short courses for



Figure 3 Case 1. Cystic fibrosis of the pancreas associated with pulmonary fibrosis and bronchiectasis. A (Left) Exaggerated hilar markings and linear infiltrations in the left upper lobe. B (Right) Four months later marked increase in infiltrations in both lungs. (Autopsy showed diffuse pulmonary fibrosis and bronchiectasis, also areas of bronchopneumonia, cystic fibrosis of the pancreas.)

two or three weeks and rarely for longer periods. The relation of such prolonged treatment to changes in bacterial flora and the occurrence of antibiotic resistance was studied. It was found

that, despite the appearance of antibiotic resistance in the nasopharyngeal flora of these patients, a satisfactory clinical response could still be obtained.

Bibliography

HYPERTROPHIC PULMONARY OSTEOARTHIROPATHY

- BAISBERGER E. Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten. *Zschr klin Med* 18 191 1891.
- BLOOM W. Pituitary Implications in Hypertrophic Pulmonary Osteoarthropathy. *Ann Int Med* 29 361 1948.
- CHARR R. and SHERSON P. C. Clubbed Fingers. *Ann J Roentgenol* 55 325 1946.
- ELLMAN P. Lungs, Bones and Joints. Letters to the Editor. *Lancet* 2 401 1955.
- FLAELL G. Reversal of Pulmonary Hypertrophic Osteoarthropathy by Vagotomy. *Lancet* 2 60 1956.
- FRIED B. M. Chronic Pulmonary Osteoarthropathy. Disputat. as a Probable Cause. *Arch Int Med* 72 565 1943.
- HANSEN J. L. Bronchial Carcinoma Presenting as Arthralgia. *Acta med Scandinav.* (Supp 766) 142 467 1947.
- HARVEY F. R. and PATTERSON L. T. Osteoarthropathy in Carcinoma of the Lung. *Arch Surg* 70 643 1955.
- HOLMES H. H. Symptomatic Arthritis Due to Hypertrophic Pulmonary Osteoarthropathy in Pulmonary Neoplastic Disease. Report of Seven Cases. *Ann Rheumat Dis* 9 169 1950.
- LOCKE, E. A. Secondary Hypertrophic Osteoarthropathy and its Relation to Simple Club-Fingers. *Arch Int Med* 15 619 1915.
- MARIE, P. De l'ostéorhropathie hypertrophique pneumique. *Revue med* 10 1 1890.
- MAUER, E. F. On the Etiology of Clubbing of the Fingers. *Am Heart J* 14 857 1944.
- MENDLOWITZ M. Measurements of Blood Flow and Blood Pressure in Clubbed Fingers. *J Clin Investigation* 20 113 1941.
- MOENIG R. C. The Production of Growth by the Action of the Pituitary Gland on the Vascular and Hemopoietic Systems. Interrelation between the Lungs and the Pituitary Gland. *Ann J Roentgenol* 54 100 1945.
- PATTERSON J. D. JR. BUCK F. and MILLER W. B. Hypertrophic Osteoarthropathy in Carcinoma of the Lung. *JAMA* 146 783 1951.
- PLABODY H. D. JR. and OLSEN A. M. Association of Bronchogenic Carcinoma and Diabetes Insipidus. Report of Cases. *Proc Staff Meet Mayo Clinic* 76 107 1951.
- RAY C. S. and FINER H. P. JR. Hypertrophic Osteoarthropathy in Pulmonary Malenancies. *Ann Int Med* 48 739 1953.
- RIVERSON C. H. and SWAN C. F. Hypertrophic Pulmonary Osteoarthropathy (Acropachy) Affecting a Patient Who Had Postoperative Myxodema and Progressive Exophthalmos. *Proc Staff Meet Mayo Clinic* 16 353 1941.

- SAMPLE T. and McCALLINE R. A. Generalized Hypertrophic Osteoarthropathy in Association with Bronchial Carcinoma. *Brit M J* 1 754 1955.
- THOMAS H. M. JR. Acropachy. Secondary Subperiosteal New Bone Formation. *Arch Int Med* 51 571 1931.
- VAN HAZEL, W. Joint Manifestations Associated with Intrathoracic Tumors. *J Thoracic Surg* 9 495 1940.
- VOGL A., BELMUEFELD S. and GUTNER, L. B. Diagnostic Significance of Hypertrophic Osteoarthropathy. *Ann J Med* 18 51 1955.
- WIERMAN W. H., CLAGETT O. T., and McDONALD J. H. Articular Manifestations in Pulmonary Diseases. *JAMA* 175 1459 1954.
- WILSON G. M. Local Circulatory Changes Associated with Clubbing of the Fingers and Toes. *Quart J Med* 21 701 1952.

DIABETES AND PULMONARY INFECTIONS

- BOLCOFF R. R., DILLON E. S., COOPER D. A., MEIER, P., and RICHARDSON R. Tuberculosis Among Diabetics. *Am Rev Tuberc* 65 Appendix 1952.
- DIAS R. J. Effect of Ketone Bodies and other Metabolites on the Survival and Multiplication of Staphylococci and Tubercle Bacilli. *J Exper Med* 98 145 1951.
- HÖBSTER, H. Untersuchungen über die durch Krankheiten hervorgerufene Änderung der Disposition zur Infektion, bzw. für Erkrankung nach Infektion. Beitrag zur Klärung der Ursache der verminderten Widerstandsfähigkeit des kranken Organismus gegen Infektion. *Deutsche Arch Klin Med* 176 507 1944.
- MOULTON S. E. Pulmonary Infection and Necrosis in Diabetes Mellitus. *Arch Int Med* 66 561 1940.
- NICHOLSON H. Suppurative Pneumonia. *Lancet* 2 549 and 675 1950.
- REPORT OF THE COMMITTEE ON STATISTICS. Recent Statistics on Diabetes. *Diabetes* 2 138 1951.
- ROOF H. F., and LUCAS W. R. Diabetes and Pulmonary Tuberculosis. With Special Reference to the Lipid Content of Diabetic Lungs. *Am Rev Tuberc.* 59 714 1959.
- REIN, E. H. Pulmonary Tuberculosis in the Aged. *Am Rev Tuberc.* 26 516 1932.
- REIN, E. H., GOLDSTEIN, S. A., and RUBIN M. Management of Nontuberculous Bronchopulmonary Suppurations. *M Clin North America* 37 91 1949.
- SUTIN D. T. Fuso-Spirochetal Disease of the Lungs. Its Bacteriology, Pathology and Experimental Reproduction. *Am Rev Tuberc* 16 584 1917.
- STEINBAUM M. M., KERN S. J. and DESKOWITZ M. Experimental Diabetes and Tuberculosis in the Dog. *Am Rev Tuberc.* 32 665 1915.
- TUTTLE W. M. and NICOLL, G. L. The Effect of Pulmonary Artery Ligation on the Healing Time of Experimental Pyogenic Lung Abscesses in Dogs. *J Thoracic Surg*, 2 60 1932.

CYSTIC FIBROSIS OF THE PANCREAS AND PULMONARY INFECTIONS

- ANDERSEN D H Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease. A Clinical and Pathologic Study *Am J Dis Child* 56:344 1938
- ANDERSEN D H and HONGES, R G Celiac Syndrome *Am J Dis Child* 77:67 1946
- ATWOOD C J., and SARGENT W H Cystic Fibrosis of the Pancreas with Observations on the Roentgen Appearance of the Associated Pulmonary Lesions *Radiology* 39:417 1947
- BAYLIN G J Pulmonary Changes in Chronic Cystic Pancreatic Disease *Am J Roentgenol* 52:417 1947
- BLACKFAN K D and MAX C D Inspissation of Secretion Dilatation of the Ducts and Acini Atrophy and Fibrosis of the Pancreas in Infants *J Ped* 13:677 1938
- BLACKFAN K D., and WOLBACH B S Vitamin A Deficiency in Infants *J Pediatr* 3:679 1933
- DICKEY L B Pulmonary Disease Associated with Cystic Fibrosis of the Pancreas *Dis Child* 17:151 1950
- DI SANT'AGNESE, P A Bronchial Obstruction with Lobar Atelectasis and Emphysema in Cystic Fibrosis of the Pancreas *Pediatrics* 17:178 1953
- DI SANT'AGNESE P A Fibrocystic Disease of the Pancreas a Generalized Disease of Exocrine Glands *JAMA* 160:846 1956
- FARBER, S Pancreatic Function and Disease in Early Life V Pathologic Changes Associated with Pancreatic Insufficiency in Early Life *Arch Pathol.* 37:738 1944
- HIRSCH E F CARBONARO L., BRIGGS A D and PHILLIPS F L Postprandial Hypolipemia of Pancreatic Fibrocystic Disease *Am J Dis Child.* 86:721 1953
- KEATS T E Generalized Pulmonary Emphysema as an Isolated Manifestation of Early Cystic Fibrosis of the Pancreas *Radiology*, 65:773, 1955
- KRABENHOFT K L and EVANS W A, Jr Some Pulmonary Changes Associated with Intracardiac Septal Defects in Infancy *Radiology*, 63:498 1954
- NADAS A S, COGAN G LANDING, B H and SCHWACHMAN H Studies in Pancreatic Fibrosis *Pediatrics* 10:319 1952
- NEUBAUER, E W D Roentgen Changes Associated with Pancreatic Insufficiency in Early Life *Radiology* 46:319 1946
- NORRIS R F., and TYSON R M The Pathogenesis of Congenital Polycystic Lung and Its Correlation with Polycystic Disease of Other Epithelial Organs *Am J Pathol.*, 23:1075 1947
- PLIGSKEN H E and SPENCE, P McH. A Case of Cystic Fibrosis of the Pancreas Associated with Chronic Pulmonary Disease and Cirrhosis of the Liver *Ann Int Med* 30:1267 1949
- ROSENDALE, T Pulmonary Changes in Fibrosis of the Pancreas *Acta Radiol* 35:233 1951
- SILVERMAN F N., and SHIRKEY H C A Fat Absorption Test Using Iodized Oil with Particular Application as a Screening Test in the Diagnosis of Fibrocystic Disease of the Pancreas *Pediatrics* 15:143 1955
- STOPPELMAN M R H and SCHWACHMAN H Effect of Antibiotic Therapy on Mucoviscidosis A Bacteriologic Study *New England J Med* 251:759 1954
- WEST J R LEVIN S M and DI SANT'AGNESE, P A Pulmonary Function in Cystic Fibrosis of the Pancreas *Pediatrics* 13:155 1954
- ZELZER W W., and NEWTON W A Jr The Pathogenesis of Fibrocystic Disease of the Pancreas A Study of 36 Cases with Special Reference to the Pulmonary Lesions *Pediatrics* 4:53 1949

Diseases of Metabolism (Concluded)

Histiocytosis with Pulmonary Involvement

INTRODUCTION

THE HISTIOCYTE is a large pale foam cell found in the reticuloendothelial system from which are derived the epithelioid and giant cells of certain inflammatory processes. Among diseases of the histiocytic or reticuloendothelial system two major disorders are recognized—one metabolic, the other, inflammatory. The metabolic histiocytoses Gaucher's disease and Niemann Pick's disease are rare hereditary diseases found almost exclusively in the young and characterized by the deposition of specific lipids in the cells. In Gaucher's disease the lipid is a cerebroside in Niemann Pick's disease the lipid is a phosphatid. These two are storage diseases the lipids being present within the cells but not in the blood. The inflammatory histiocytoses although encountered chiefly in the young are also seen in older persons. The diseases are characterized by eosinophilic granulomatous changes in various organs and tissues of the body. The inflammatory histiocytoses are Hand Schuller Christian's disease Letterer Siwe's disease eosinophilic granuloma of bone and on rare occasion eosinophilic granuloma limited to the lung. Lightwood prefers the term histiocytic reticulo endotheliosis because it is still open to question whether the condition is inflammatory. In line with this view Bodian speculates that these syndromes may be examples of histiocytic neoplastic processes varying from solitary or multiple focal lesions to a diffuse and frankly malignant disorder of the reticulo endothelial system.

The inflammatory disorders of the histiocytic system differ in several respects from the primary

lipid metabolic disorders. In Hand Schuller Christian's disease there is often present an increase in cholesterol and cholesterol esters in the blood as well as in the tissues. The increase in lipid content however is a secondary phenomenon and is encountered chiefly in advanced stages of the disease. It is not a basic feature of the disease. Letterer Siwe's disease is a nonlipid histiocytosis but an increase in lipid content may also be present in this condition. Cases of Letterer Siwe's disease have been described in which the lipid content of the tissues was quite high although the disease had existed for only a short time. Eosinophilic granuloma of bone may affect one several or many bones. According to Jaffe and Lichtenstein who coined this term the condition represents the mildest expression of inflammatory histiocytosis. Very few well documented cases are on record of eosinophilic granuloma limited to the lung.

In the initial stages of the various inflammatory histiocytoses mentioned the pathologic changes may be quite similar but the clinical manifestations often show considerable variation and overlapping as exemplified in titles such as the following: Reticulogranuloma Report of a Case of Eosinophilic Granuloma of Bone Associated with Nonlipoid Reticulosis of Skin and Oral Mucosa Under the Clinical Picture of Hand Schuller Christian Disease or Histiocytic Granuloma of Skull (Triphasic Clinico Pathologic Syndrome Previously Termed Letterer Siwe's Disease Hand Schuller Christian Disease and Eosinophilic Granuloma). The several forms of inflammatory histiocytoses apparently represent different facets of a single disturbance. At one extreme usually seen in infancy one

meets with acute forms of Letterer-Siwe's disease, at the other, one meets with chronic, localized eosinophilic granuloma of bone encountered more often in older persons. Intermediate, subacute and chronic variants are seen at all ages, especially in later childhood. These are represented most often in Hand-Schüller-Christian disease. The monistic concept of the reticulo-endothelioses originally proposed by Wallgren, is subscribed to by most investigators in the field.

To simplify the discussion, possibly at the expense of oversimplification, each disorder will be defined briefly and the pulmonary manifestations described for the group as a whole. But before doing so, it is in order to mention a form of lipid pneumonia characterized by interstitial fibrosis and, histologically, by the presence of foamy monocytes containing cholesterol. The underlying cause in the majority of cases is tissue injury, although distinct evidence of the latter may not be apparent. This type of localized lipid-filled granuloma is not demonstrably part of a systemic disease. There is reason to suspect, however, that in some cases it represents an abortive form of a basically widespread disease.

✓ ENDOGENOUS LIPID PNEUMONIA

In this condition, fatty changes, consisting largely of cholesterol and its esters, are found in association with chronic degenerative pulmonary diseases. The amount of fat demonstrable histologically varies in different pathological states. It is not found in acute pulmonary disease but is present in varying amounts in tuberculosis, chronic bronchiectasis, chronic abscesses and, most often, in association with carcinoma of the lung. In the presence of a major underlying disease, such as those mentioned, the lipid changes are of incidental interest. But when the lipid deposition dominates the picture or when the nature of the underlying disease is not readily ascertainable, the finding of massive deposits of fat in the tissues provokes speculation. Endogenous lipid pneumonia, a term suggested by McNamara and Haslewood, is also known as "cholesterol pneumonia," "foam cell pneumonia," "chronic pneumonitis of the cholesterol type" and by several other nomenclatures.

The lack of a precise definition of the condition is an index of its ill-defined nature. Although endogenous lipid pneumonia is to be distinguished from oil aspiration pneumonia, due to excessive intake of mineral oil or oily nose drops by persons with defective cough reflexes, a sharp distinction is not always possible. In fact, there is reason to believe that many of the reported cases of endogenous lipid pneumonia represent, in reality, instances of oil aspiration in patients in whom a sufficiently detailed history is not obtainable. Davis cited six cases who, at operation, were found to have "localized" or "segmental" lipid pneumonia. Before operation the diagnosis was carcinoma. Three of the patients gave a history of ingestion of large quantities of mineral oil for constipation. One patient had a long history of the use of oily nose drops and one patient, a high altitude aviator, used petroleum jelly around his nose and mouth to make the mask fit better. The sixth patient, for want of a history of oil aspiration, fitted into the group of endogenous lipid pneumonia. Recently a patient was treated at the Montefiore Hospital in whom a lipid pneumonia caused a localized granuloma simulating a neoplasm. But only after the mass was excised and the tissue showed a gelatinous tumor with lipid laden macrophages was a history obtained that the patient had been using oily nose drops for many years.

Robbins and Sniffen reported eleven cases of "chronic pneumonitis of the cholesterol type" treated surgically. The outstanding feature of the pneumonia was the presence of deposits of cholesterol and cholesterol esters in the air spaces, in the absence of coexistent lung disease. The evidence did suggest, however, that some obstruction of the smaller bronchi or bronchioles was often present and that this might have been a determining factor in laying the background for the type of reaction observed. Five years later Waddell, Sniffen and Whytehead concluded that the endogenous variety of lipid pneumonia is due to local acidosis in an injured or infected tissue causing an adverse effect upon the colloidal lipids. They found that in rabbits the intratracheal inoculation of either *Pasturella pseudotuberculosis* or *Klebsiella pneumoniae* resulted in

interstitial pneumonitis in which large numbers of macrophages were seen. In the presence of induced lipemia and hypercholesterolemia these cells became laden with cholesterol and fat producing the picture seen in humans. According to these investigators endogenous lipid pneumonia and aspiration lipid pneumonia may be distinguished by the fact that the microscopic picture in the former shows a uniform distribution of lipid throughout the cytoplasm of the macrophages and the droplets are extremely minute.

Of particular interest is the fact that the roentgen changes of lipid pneumonia whether endogenous or exogenous may resemble closely those of primary pulmonary neoplasm as illustrated by the following case.

Case 2 Female—Age 50

The patient became ill in March 1953 with cough, expectoration and wheezing. She stated that she seldom had coughed previously. There was no fever, shortness of breath, hemoptysis or chest pain. The patient did have a sense of soreness over the

right upper chest and had lost a moderate amount of weight. The past history was unrevealing. She had been a light smoker and used nose drops on rare occasions. She had no difficulty in swallowing and had no major operations.

The physical and x-ray findings of the chest revealed a dense homogeneous consolidation occupying the entire right upper lobe (Figure 4A). Bronchoscopy showed stenosis of the right upper lobe bronchus. Smears taken failed to reveal tumor cells or acid fast bacilli. On July 21, 1953 an exploratory thoracotomy was done by Dr. Morris Rubin. The right upper lobe was found completely consolidated, the middle and lower lobes were free of disease. There were enlarged hilar lymph nodes. The lesion appeared malignant and a right pneumonectomy was done which the patient tolerated well.

Gross examination reveals almost the entire upper lobe replaced by a firm tissue mass (Figure 4B). The lower lobe was collapsed and no areas of consolidation or increased consistency were found. The surface of both lobes was smooth and glistening. No adhesions were noted nor were there any interlobar adhesions. The bronchial tree contained some mucoid material but no evidence of tumor. The hilar

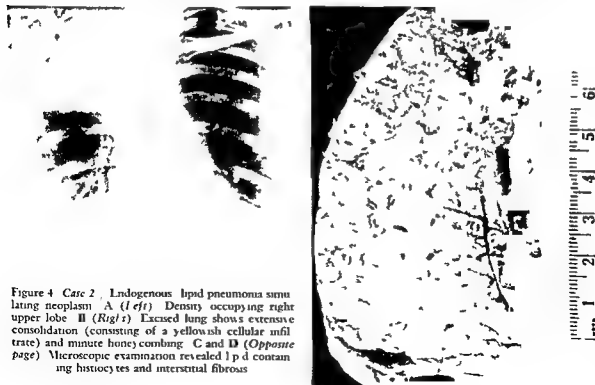


Figure 4 Case 2. Endogenous lipid pneumonia simulating neoplasm. A (left) Density occupying right upper lobe. B (right) Excised lung shows extensive consolidation (consisting of a yellowish cellular infiltrate) and minute honeycombing. C and D (Opposite page) Microscopic examination revealed lipid containing histiocytes and interstitial fibrosis.

Lymph nodes were small, spongy and anthracotic. On section, there was an extensive consolidation of the entire lobe. The consolidation consisted of a yellowish cellular infiltrate through the parenchyma. There was no evidence of tumor tissue seen anywhere in the lung. Some of the consolidated areas were softer in consistency and revealed areas of necrosis. The microscopic findings confirmed the gross appearance of a lipid pneumonia (Figures 4C and D).

Recently I had an opportunity of demonstrating that the finding of a lipid pneumonia does not necessarily imply an irreversible reaction. A man of fifty-eight presented himself with a six-month history of cough, malodorous but not distinctly foul expectoration, loss of thirty pounds in weight, pain in the right chest and weakness. The past history revealed a seizure of influenzal pneumonia after World War I and periodic recurrences of hay fever and hives. The patient had considerable cough and moderate dyspnea

during the preceding five years. The physical examination was not revealing. The chest x-ray showed a large, fairly well circumscribed density in the right upper lobe. Bronchoscopy revealed a number of atypical cells. In the absence of a clear-cut history to suggest pulmonary suppuration, carcinoma was suspected and thoracotomy done.

Upon entering the pleural cavity, a moderately hard mass was found in the right upper lobe. It was densely adherent to the chest wall over a wide area. Mobilization, even along an extrapleural plane, was not feasible. It was felt that the mass was malignant and that a radical excision was too formidable an operation for the patient to tolerate. A piece of tissue was removed from the mass for histologic study. The lung biopsy revealed severe fibrosis of the pulmonary parenchyma with whorls and nodules of fibrous tissue, also thickening of the alveolar septa. Very

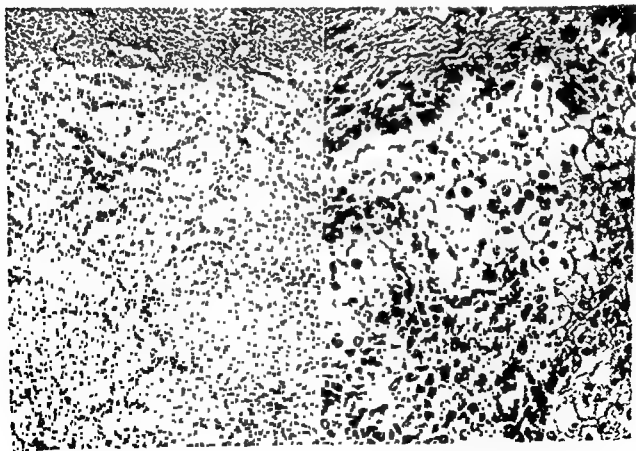


Figure 4C and D (See legends on pages 34 & 35)

prominent were numerous groups of large vacuolated foam cells containing one or two small, round nuclei. These cells were closely packed in clumps and appeared to be located in the alveolar lumens. They represented large lipid filled macrophages. The picture was in keeping with lipid pneumonia with organization. There was no evidence of neoplasia.

The patient was placed on intensive antibiotic treatment. During the following eight months there was slow but steady decrease in the size of the mass and the patient made a parallel degree of symptomatic improvement with gain of forty pounds in weight. I have encountered two additional patients who revealed at operation, apparently nonresectable pulmonary carcinomas. Lung biopsies revealed lipid pneumonia and fibrosing pneumonitis. The subsequent course of events in both cases extending over three and nine-year periods, respectively, excluded the possibility of malignant neoplasms.

GAUCHER'S DISEASE

This is a rare familial condition characterized by the accumulation of *lécithin*, a cerebroside in the cells of the reticuloendothelial system. In a study of twenty nine cases by Medoff and Byrd the ages ranged between two and one half and fifty six years at the time of the first visit to the Mayo Clinic. The, so called Gaucher cells appear as wrinkled swollen reticular cells infiltrated with lipid found chiefly in the spleen, liver, lymph glands and bone marrow. The clinical features of Gaucher's disease are an insidious onset, a protracted course with hepatosplenomegaly but normal liver function, pigmentation, a yellowish brown pigmentation of the skin and sclera and skeletal defects especially of the femora and other long bones. Hypochromic anemia, leukopenia, thrombocytopenia and a tendency to hemorrhage are associated phenomena.

NIEMANN PICK'S DISEASE

This is also a rare metabolic disturbance occurring chiefly in Jewish female infants. I except for the more widespread involvement and gastrointestinal disturbances leading to marked malnutrition, the condition resembles closely Gaucher's

disease. Death occurs usually before the age of three years from cachexia or an intercurrent infection. In Niemann Pick's disease there is marked physical and mental deterioration, the latter akin to that met in Tay-Sachs infantile idiocy. The lipid found in the tissue and which is pathognomonic of the disease is sphingomyelin, a phosphatid. The following report of a patient treated at the Montefiore Hospital is of unusual interest since it concerned an adult with lipidosis, closely resembling Niemann Pick's disease.

Case 3. Male—Age 53

White Jewish patient was rather dull, backward and sickly as a child and did not speak until he was seven years of age. The patient was admitted to the Montefiore Hospital on December 7/31 with a history that ten months previously he developed weakness, easy fatigability and a hacking cough productive of moderate amounts of sputum, at times blood tinged. The patient soon developed dyspnea and orthopnea and on several occasions he had substernal pain which radiated to the left shoulder. The dyspnea, cyanosis increased and there soon appeared hepatosplenomegaly and evidence of cardiac failure. X rays of the chest showed diffuse pulmonary fibrosis (Figures 5A and B). Biopsy of a lung specimen revealed collections of intraalveolar foam cells. A complete study including various laboratory tests was unrevealing. The patient continued to have cough, productive of tenacious sputum at times bloody, and left sided chest pain. The patient became increasingly more dyspneic, cyanotic, stuporous, lapsed into coma and died.

The postmortem findings revealed, in brief, massive involvement of the lungs, liver and spleen by lipid filled histiocytes (Figures 5C and D). Relatively fewer of these cells were found in the adrenal cortex, bone marrow and lymph nodes. An abnormal pigment was found in these organs as well as in the reticuloendothelial system. Chemical

analysis of the lipid in the lungs, liver and spleen pointed to Niemann Pick's disease. Although large accumulations of this lipid were found in the liver and spleen, it was in smaller concentration than that noted by others in the tissues of infants with Niemann Pick's disease. It was concluded that the lipidosis in this patient was related to Niemann Pick's disease though not identical with it.



Figure 5 Case 3. Histologic lesions A (Upper left) Diffuse, reticular striations throughout both lungs B (Upper right) Lung The alveoli are filled by lipid-containing macrophages and the septa are sclerotic C (Lower left) Lung The intraalveolar foam cells are apparent in this section (Similar histiocytes were found in the liver, spleen, adrenal cortices, bone marrow and lymph nodes, disease in keeping with Niemann-Pick's disease) (From Terry, Sperry and Brodoff *Am J Path.*, 30 263, 1954)

HAND SCHULLER CHRISTIAN'S DISEASE

DISEASES OF METABOLISM (CONCLUDED)

This metabolic disturbance is characterized by yellow granulomatous nodules in the skin mucous membranes and internal organs. In a review of eighty four reported cases of Hand Schuller Christian's disease, Gross and Jacob noted that in twenty six the presence of foam cells was not mentioned and in nine necropsy and biopsy material showed no foam cells. With chronicity the foam cells are replaced by fibrous tissue which may or may not contain variable amounts of eosinophils. As mentioned in associated fat ure is cholesterol infiltration of the tissues. The disease begins insidiously in childhood but it may attack infants as well as aged. The classical triad found in Hand Schuller Christian's disease which distinguishes it clinically from other histiocytoses is a bizarre combination of exophthalmos due to retro orbital proliferation of granulomatous tissue, diabetes insipidus due to pituitary gland involvement and cystic lesions in the skeletal system due to destruction of bones.

Case 4 Male—Age 35

In the course of a pre employment chest x ray patient was found to have symmetrical infiltrations throughout both lungs also prominence of the hilar shadows. The heart was normal in size and configuration. Sputum examinations failed to reveal acid fast organisms. Other laboratory tests were noninformative. In the absence of an occupational history a diagnosis of diffuse pulmonary fibrosis, etiology unknown was made. The patient was not seen until eight years later when he returned to the clinic complaining of general weakness and progressive shortness of breath and more recently slight cough and hoarseness.

Physical examination at this time revealed evidence of considerable loss of weight dyspnea after the slightest exertion and cyanosis of the lips and cheeks. Palpation of the scalp revealed in the right parietal region a slightly tender irregular area of depression of the osseous wall which the patient noted he had had for about a year. The neck veins were engorged. The liver was enlarged and there was slight pretibial edema. The chest x ray now disclosed extensive interstitial fibrosis throughout both lungs from apex to base. The heart was moderately enlarged with definite prominence of the pulmonary conus and enlargement of both ventricles (Figures

6A B and C). An x ray of the skull disclosed a large irregular area of bone destruction in the right parietal region (Figure 6D). Several small cystic areas of bone destruction were also found in the upper two thirds of the right femur also evidence of bone destruction in the left femur and left tibia.

Biopsy of the lesion of the right parietal bone revealed a general histologic pattern of a lipid granuloma of the skull consistent with Hand Schuller Christian's disease. The patient showed evidence of increasing cardiac decompensation and died. A complete autopsy was not obtained.

LEITERER'S DISEASE

This is a nonhereditary nonfamilial form of histiocytosis of unknown cause. One form appears to follow acute respiratory or other infections but this is probably an incidental or secondary occurrence. The disease attacks infants almost exclusively. With few exceptions the disease is acute with a rapid and fatal course. There is a generalized hyperplasia of the reticuloendothelial cells with small tumor formations in the spleen liver lymph nodes thymus gland and bone marrow showing hemorrhagic tendency. As a rule there is no lipid storage in the cells if present it is a secondary phenomenon. With chronicity the disease takes on many features of Hand Schuller Christian's disease with increasing deposition of cholesterol in the histiocytes. The outstanding clinical features are marked weakness irritability and a tendency to bleeding. The physical findings reveal hepatosplenomegaly lymphadenopathy localized skeletal tumors and progressive anemia.

Case 5 Female—Age 20 months

At six months of age the infant was first treated for chronic discharging ears, also a macular papular eruption of the skin. The condition improved but six months later the infant was readmitted to the hospital because of a recurrence of the skin ailment which was suspected to be a seborrheic dermatitis or tubercular. A chest x ray revealed infiltrations throughout both lungs especially the upper lobes (Figure 7A). In view of the fact that the infant's father had been treated for tuberculosis it was suspected that the infant had inherited tuberculosis. However the Mantoux test was negative.

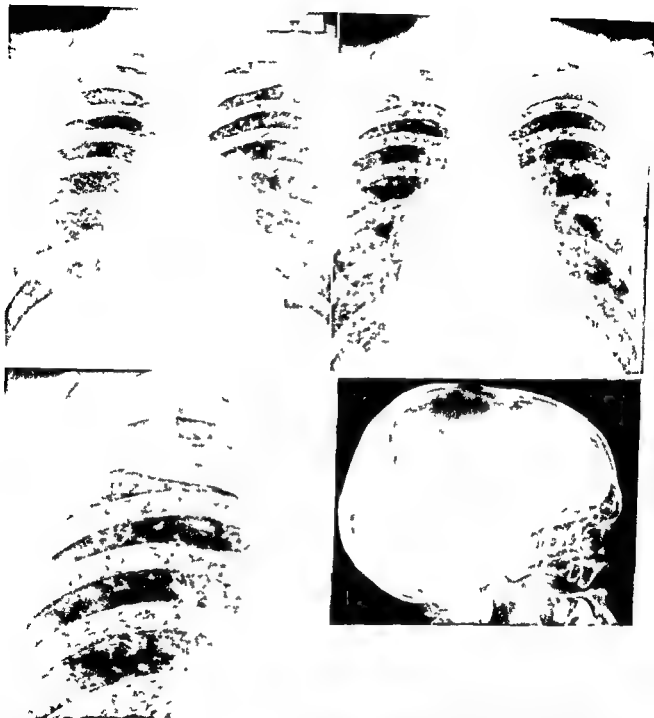


Figure 6 Case 4 Histiocytosis with pulmonary and skeletal lesions: A (Upper left) Diffuse reticular infiltrations throughout both lungs with minute cystic areas B (Upper right) Seven years later reticulations more conspicuous heart enlarged C (Lower left) Lung detail showing fine honeycombing D (Lower right) Skull Geographic defect of right parietal bone (Biopsy of parietal bone showed microscopically histiocytes foam cells and other features consistent with Hand Schuller Christians disease) (From Schneerson and Schneider *Ann Int Med* 30:842 1949)



Figure 7 Case 5 Histiocytosis with pulmonary and visceral lesions A (Left) Faint miliary stippling in both upper lobes B (Middle) Five months later diffuse lace like reticulations with minute honeycombing of both lungs left sided pneumothorax (spontaneous) with catheter in situ (Autopsy showed histiocytosis of lungs with numerous blebs on surface histiocytosis of skin liver, spleen other features in keeping with Letterer-Siwe's disease)

and repeated examination of gastric lavages and spinal fluid failed to reveal acid fast organisms. At this time the liver and spleen were found to be enlarged, the cholesterol was 500 mgs. %, cholesterol esters 40. Other laboratory tests were noninformative. The diagnosis was Hand-Schüller-Christian's disease.

The infant was readmitted at the age of twenty months. At this time there was found severe pyoderma purpuric lesions of the scalp and seborrheic dermatitis, cervical adenopathy and hepatosplenomegaly. A liver biopsy was reported as showing cholangiectatic hepatitis. A laparotomy revealed a dilated common bile duct but no hepatic obstruction. The drainage from the abdomen was inadequate and shortly thereafter the patient had a left-sided spontaneous pneumothorax which was decompressed with a drainage tube (Figure 7B). The course of the disease was progressively downhill and the infant died.

At autopsy the liver was enlarged, the common duct was dilated and there was a soft inspissated bile stone in the hepatic duct. Dilated bile ducts contained inspissated bile. The lungs were airless with blebs on the surface. The left lung was collapsed and revealed advanced consolidation of both organs. The pleural surface of the right lung was smooth clear shining with numerous blebs on the surface. The left lung was rough where an adhesion tore

The cut section revealed airless solid lungs with numerous air cysts throughout, also scattered velvety areas. Microscopic examination revealed elements of reticuloendothelial cells with histiocytes involving the skin, liver and lungs. Isolated histiocytes were found in the spleen. Stains revealed fat-containing histiocytes in the liver and lung. It was felt that the histologic picture was in keeping with Letterer-Siwe's disease although there were features suggestive of a transitional stage between the latter and Hand-Schüller-Christian's disease.

EOSINOPHILIC GRANULOMA OF BONE

Eosinophilic granuloma of bone is a granulomatous condition in which the affected bones contain large numbers of eosinophilic cells giving rise to cystic rarefactions. The bone localization represents a limited form of inflammatory histiocytosis. Jaffe and Lichtenstein, also Otani and Ehrlich believe that the condition represents a peculiar inflammatory reaction, the presence of lipid-containing macrophages and fibrotic reaction being determined by the chronicity of the disease. As mentioned, eosinophilic granuloma of bone may be present in association with visceral involvements including involvement of the lungs. Phillips reported two cases of intrathoracic "xanthomatous" new growths and collected

three similar cases in the literature. The tumors were solid firm oval and originated from the costovertebral groove of the thoracic cage. They were nonmalignant. The structure of the tumor was characterized by great abundance of lipid globules in large swollen polyhedral cells and smaller spindle shaped cells.

EOSINOPHILIC GRANULOMA OF THE LUNG

In this disease pulmonary histiocytosis is present without demonstrable skeletal or visceral involvements. The pulmonary lesion or lesions are found accidentally either at autopsy or on biopsy of lung tissue. Lichtenstein suspects that such isolated pulmonary lesions of eosinophilic granuloma are accompanied by visceral lesions which are momentarily inapparent or may become manifest later. Honeycomb lungs to which reference will be made later probably fall in the same category. More perplexing is the differentiation between limited eosinophilic granuloma of the lung and endogenous lipid pneumonia described previously in which an accompanying disease or an obvious cause of tissue injury is not demonstrable. In the condition under consideration it is presumed that the lipid accumulation in the lung is a forme fruste of a systemic disease. But there is still much to be learned about this disease.

In one type of eosinophilic granuloma of the lung a solitary tumor mass is found which on removal shows the histologic features of a histiocytosis. Scott and co workers described such an occurrence in a thirty four year old woman. The chest x ray had shown a circular circumscribed lesion in the right cardiophrenic angle. A lung tumor was suspected and removed. The mass was found to be the size of a large lemon completely contained within the lobe. Histological examination revealed oval or spindle shaped cells with small groups of xanthoma cells. There was no evidence of a generalized metabolic disturbance as manifested by diabetes, hypercholesterolemia or lipemia. There were no xanthomatous lesions in the skin and no osseous changes. The authors believed that the tumor represented either an xanthomatous deposit of a primary nature or xanthomatous replacement

of an underlying neoplasm with no identifiable remnants.

Lacley and associates reported two histologically proved cases of eosinophilic granuloma limited to the lungs with somewhat unusual features. In their cases the disease was bilateral diffuse and of a peculiar nodular quality. Biopsy of lung tissue showed granulomatous lesions not sharply circumscribed showing fibrous tissue reaction, pigment laden macrophages and histiocytes. Eosinophils were a prominent feature being present as scattered individual cells as well as in sheets and in large clumps. According to the authors the picture was that seen in eosinophilic granuloma of bone. Two similar cases were reported by Mazzitello. In one the chest x rays showed diffuse bilateral nodular infiltrations. In the other the chest x rays revealed also numerous areas of rarefaction which were believed to represent multiple small cavities. The presence of eosinophilic granuloma was confirmed in both cases by lung biopsies. Of additional interest was the moderate degree of clearing of the pulmonary lesions with ACTH treatment.

PULMONARY LESIONS IN THE HISTIOCYTOSIS

The pulmonary manifestations of diseases of the histiocytic system provide an interesting field of study from the viewpoint of the pulmonary findings. The lungs often serve to highlight the unified nature of the disturbance since comparable and overlapping changes are present in the several forms of the disease. Usually the lungs are implicated as part of a widespread disease but as mentioned the disease may be limited to or mask its first appearance in the lungs. In an analysis of eighteen reported cases of Letterer-Siwe's disease Orchard found mention of pulmonary reticulosis in ten and in six others there were questionable changes. Some years ago Chesler and Kugel of the Montefiore Hospital compiled data on fifty reported cases of Hand-Schüller-Christian's disease including many instances in which the lungs were involved.

In Gaucher's disease the lungs are seldom affected but when changes do occur they may be quite striking. Myers reported the case of a young girl in whom the lungs showed roentgen

logically delicate reticulations extending fanwise from the hilar regions into the mid portions of both lungs. The child died and autopsy disclosed large hilar lymph glands and an infiltrative process extending into and invading the lungs. Histological examination of the tissue revealed the lymph nodes and lung parenchyma permeated with Gaucher cells. Myers referred to another reported case in which Gaucher cells were found in the sputum.

In a lucid description of the pulmonary manifestations of Niemann Pick's disease, Thannhauser draws attention to the frequency of bronchitic symptoms and the tendency to small pneumonic infiltrations associated with elevation of temperature. The appearance of the chest x-ray is in keeping with milary tuberculosis. Histologic examination of tissues reveal the bronchi filled with exudate containing leukocytes and Niemann Pick cells. The interstitial tissues show accumulation of lipid. Thannhauser believes that if it were possible to examine the sputum with the possibility of the existence of the disease in mind the diagnosis of Niemann Pick's disease might be made from the appearance of the cells alone.

A brief note on treatment may be in order. Although recovery is possible even in the acute forms of the disease the prognosis is usually poor except in cases of eosinophilic granuloma of bone which has a decided tendency to heal spontaneously. Lightwood and Tizard found that of approximately forty reported cases of Letterer-Siwe's disease there were six including one cited by these investigators in which apparent recovery took place. Large tumor masses often respond to radiotherapy because the cells characterizing this group of diseases are highly radio sensitive. Steroid treatment has met with variable degrees of success. Antifoliate treatment is indicated because of the possibility that the symptoms may be partly due to infection to which the patients are unusually susceptible.

ROENTGENOLOGY OF PULMONARY LESIONS IN HISTIOCYTOSIS

From a review of a sizeable number of reported cases of inflammatory histiocytosis in-

cluding a few personally observed it is possible to differentiate several roentgenologic patterns of the disease providing of course the basic disturbance is known or suspected. The cystic pattern to be described later may be sufficiently suggestive to make one think of the possible presence of a histiocytic disease in differential diagnosis in the absence of systemic lesions. In Letterer-Siwe's disease one is apt to see milary or patchy infiltrations evenly dispersed in both lungs, especially the upper halves. Occasionally large irregular consolidations are noted. The former simulate milary tuberculosis the latter bronchopneumonia. There is often a remarkable similarity of the roentgen markings in Letterer-Siwe's disease with those found in association with cystic fibrosis of the pancreas. Since one is usually dealing with a disease of infancy the differential diagnosis of the two diseases is always a consideration.

In the chronic form of Hand-Schüller-Christian's disease one is apt to find linear fibrotic striations permeating both lungs. The condition is in keeping with diffuse interstitial pulmonary fibrosis. Hand-Schüller-Christian's disease may also manifest itself in small or large irregular densities of granular infiltration with hazy margins on a background of emphysematous lung tissue. The picture brings to mind sarcoidosis although the latter rarely undergoes true cystic changes rather emphysematous bullae and bleb formations. Fungous infection is another disease that may be considered in the differential diagnosis. As mentioned previously circumscribed lipid pneumonia may simulate neoplasms. Inasmuch as the granulomas enlarge through increasing deposition of lipid substance rather than cell division such xanthomas are not true neoplasms. Instances have been described where it was suspected that the condition had undergone sarcomatous changes. More likely as indicated earlier in the chapter the lipid changes are secondary to an underlying malignancy.

Probably the most striking roentgen changes encountered in the inflammatory histiocytoses are cystic or honeycomb lungs. Variable degrees of diffuse fibrosis of the organs are also present. These small cysts usually not exceeding 1 cm in

diameter, are seen most often in patients with eosinophilic granuloma of bone. The condition is also encountered in Letterer-Siwe's disease as well as in Hand-Schüller-Christian's disease. In one of four cases, reported by Forsee and Blake, the chest x-ray showed bilateral air and fluid filled cysts, measuring 2 to 3 cm in diameter, throughout both lungs. There was also a tumor of the left lower bronchus. Excisional biopsy of lung, bronchial tumor and other tissue showed lipid granulomatous lesions. Honeycomb lungs may be found in association with biliary cirrhosis of infancy, pituitary disorders (diabetes insipidus), tuberous sclerosis and allied neurocutaneous disorders as well as in scleroderma. Rarely is honeycomb lung due to faulty development. In an instance of this type, which I reported elsewhere, there were found at autopsy multiple small cysts in both lungs associated with a patent ductus arteriosus, congenital aneurysms of the pulmonary arteries and anomalous coronary arteries.

It may be mentioned at this juncture, that diabetes insipidus may be found not only in association with the histiocytoses but also in the presence of sarcoidosis, various infections, trauma, tumors and other conditions. On rare occasion as in a case reported by Freud diabetes insipidus is associated with interstitial pulmonary fibrosis. The problem arises whether the finding of the latter, in the absence of stigmata of a past or present disseminated disease, may not represent a 'forme fruste' of a more widespread occult disturbance. This possibility is mentioned on several occasions in these pages, not only under the circumstances mentioned but also when indeterminate, diffuse fibrosis of the lungs occurs in the absence of any other demonstrable disease. A case in point will be cited shortly which prompts such a speculation (Case 6).

Histiocytosis is probably the most frequent systemic disease associated with honeycomb lungs, especially in children. MacDonald and Shanks described seven cases of honeycomb lungs in children. The authors considered "cancerthomatosis" as the most likely cause. I have encountered cystic lungs as a late event in chronic, diffuse, interstitial pulmonary fibrosis of inde-

terminate etiology (see Chapter 6). It should be noted however, that the examination of tissue may not reveal characteristic histiocytic cells unless the sections are properly prepared. This presupposes that the examiner is aware of or suspects the possible presence of a histiocytic disease.

allow the escape of air into the interstitial stroma and subpleurally. Rupture of a pleural bleb gives rise to spontaneous pneumothorax which may be recurrent. Long standing pulmonary disease associated with hypertension of the lesser circulation may give rise to chronic cor pulmonale, another frequent complication. These several features are combined in the following patient whose course I followed for a number of years. Unfortunately, the nature of the underlying disease could not be ascertained even after the examination of the lungs at autopsy, which was limited to the chest. This case is included here primarily as an excellent example of honeycomb lungs. The pathologist suspected a congenital cystic lung although the clinical course of the disease appeared to be more in keeping with an acquired disease.

Case 6 Male—Age 37

A white male became ill on September 11, 1940 when he suddenly developed pain in the chest, lost his breath and couldn't walk. The patient was hospitalized and a bilateral spontaneous pneumothorax was found with a small pneumothorax on the right side and a 50 per cent collapse of the left lung. The pneumothorax gradually disappeared from both pleural cavities but the patient continued to have difficulty in breathing although not to a disabling degree. He had occasional respiratory infections with cough and expectoration.

Early in 1947 he had a respiratory infection. At this time examination revealed evidence of clubbing of the fingers, moderate cyanosis and dyspnea on exertion. Chest x-rays revealed innumerable, minute cystic changes throughout both lungs from apex to base. It gave the lungs a fine honeycomb appearance brought out best in tomograms (Figures 8A and B). Various laboratory tests including a survey of the skeletal system revealed no abnormal findings. In the course of the following two years the patient developed increasing

dyspnea orthopnea enlargement of the liver swelling of the feet and venous engorgement indicative of right heart failure of which he died

Autopsy revealed the lungs voluminous with moderate fibrous thickening of the pleura The cut section presented an extremely interesting appearance It was sponge like due to the presence of innumerable cystic structures varying in size from several mm to 3 to 4 cm in greatest diameter The walls of the cysts were thin measuring less than 1 cm in thickness They were apparently empty and had a smooth glistening lining None appeared to be infected Occasional cysts revealed ill defined intramural yellow or pink patches The larger cysts were mostly in the upper lobe (Figure 8C) The relatively uninvolved parenchyma presented a spongy architecture due to compensatory emphysema The bronchi revealed the mucosal lining smooth pink in color no evidence of dilatation, and distinct bronchial communications could not be demonstrated The pulmonary arteries were slightly to moderately dilated but thin walled

Microscopic examination revealed the lung parenchyma for the most part replaced and distorted by cystic structures of varying size many of which were multiloculated (Figure 8D) The cysts communicated freely with one another The walls were formed by cellular connective fibrous tissue In other areas the walls were composed of dense col-

lapsed or almost hyalinized connective tissue In some areas strands and bundles of smooth muscle fibers were present The lining of the cysts varied from tall cylindrical ciliary epithelium to cuboidal epithelium to a single layer of flat epithelium and in many areas there was no epithelial lining at all At some points the cystic structures were lined by a stratified liver composed of rather small indifferent epithelial cells which superficially but not actually resembled stratified squamous mucosa A few of the cystic structures contained material composed of degenerated macrophages edema fluid and a few polymorphonuclear leukocytes Most of them however were empty and apparently well aerated One section disclosed a free communication between a bronchiole and one of the cystic structures The cysts were empty of fluid and well aerated In a few areas small scattered collections of lymphocytes were seen adjacent to cystic structures but no significant degree of inflammation The bronchi were unremarkable and revealed no evidence of bronchiectasis A striking feature seen in all the sections was a moderate to marked degree of intimal thickening of small pulmonary arteries and arterioles The larger pulmonary arteries revealed only slight arteriosclerosis Fat stains disclosed a few scattered pseudophylic deposits in some of the denser fibrous areas

Amyloidosis of the Lungs

Amyloidosis is a disease caused by a disturbance of protein metabolism Amyloid is a translucent and structureless substance which can be distinguished by its affinity for iodine Congo red and other metachromatic dyes In spite of considerable overlapping four varieties of amyloidosis are recognized clinically according to the classification proposed by Remmann Roucky and Eklund (1) A primary atypical type (2) A much more common secondary type in association with preexisting tuberculosis bronchiectasis emphysema osteomyelitis draining sinuses and other suppurative diseases (3) A type simulating

the primary form but found in association with multiple myeloma and (4) A type characterized by localized deposits of amyloid causing tumor formation This type is found chiefly in the respiratory tract especially the larynx but also the heart skin and other sites

Remmann and co workers believe that primary and secondary amyloidosis have much in common Mesenchymal tissue and parenchymatous organs are affected in both and both may be systematized In their opinion the primary form is distinguished chiefly by the absence of a discernible cause by the predominant involvement of

Figure 8 Case 6 Honeycomb lungs A (Upper left) Diffuse reticulations of both lungs B (Upper right) Tomogram showing detail C (Lower left) Lung Innumerable cysts more conspicuous in the upper lobe D (Lower right) Lung Diffuse interalveolar fibrosis many small cysts (Death due to chronic cor pulmonale)

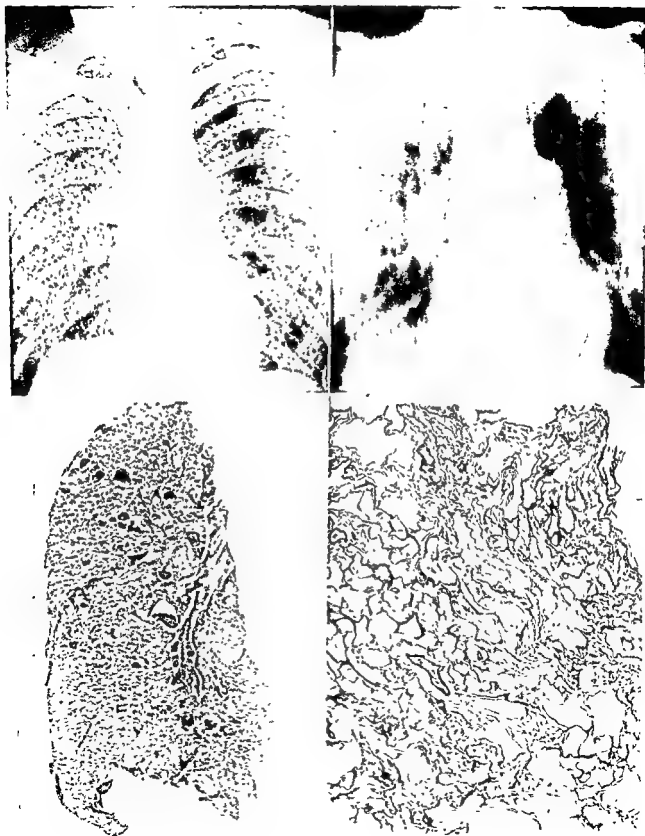


Figure 8 (See legend on preceding page)

the heart gastrointestinal tract lung and muscle and by its slow progression. Secondary amyloidosis is characterized by a more rapid development and a predominant localization in the spleen liver and kidneys. The authors believe that amyloidosis a form of proteomiosis has certain features in common with other retention or storage diseases such as glycogenosis and lipidosis.

The primary or atypical form of amyloidosis was first brought to the attention of physicians by Lubarch in 1929. He described three cases in two of which the lungs were involved. In 1935 Perla and Gross reported three additional cases from the Montefiore Hospital New York. One a female of fifty three died with signs of congestive heart failure. An underlying carcinoma of the lung was suspected. At autopsy the left lung showed extensive atelectasis involving the entire lower lobe and the lower part of the upper lobe. A positive test for amyloid was obtained with Lugol's solution. Microscopic examination revealed a peculiar homogeneous material in the walls of many of the blood vessels and the presence of amyloid material in the alveolar walls confirmed by Congo red test. In addition the patient had macroglossia due to amyloidosis of the tongue and amyloid infiltration of the heart colon diaphragm and uterus. A recent review on primary systemic amyloidosis by Mathews refers to ninety eight reported cases. In thirty five the lungs were involved.

In most instances atypical amyloidosis involves the larynx trachea or main bronchi in a few the lung parenchyma. Whitwell reported the case of a forty eight year old man in whom the diagnosis was made from bronchoscopic study. The author reviewed pertinent findings of ten additional cases of amyloid tumors of the lower respiratory tract reported in the literature. Since the disease is found chiefly in elderly men the condition has to be differentiated from bronchial carcinoma. Weissmann Clagett and McDonald found reports of three cases of localized amyloid disease of the lung and added a fourth case of their own. The particular case was treated by pneumonectomy. The operation was performed in an attempt to establish the cause of repeated episodes of hemoptysis. The disease was found to

involve the right main bronchus its branches and the corresponding branches of the pulmonary vessels and the root of the lung. Later in the same year another patient was referred to the same institution for treatment of a tumor of the right lung. Bronchoscopic examination did not disclose a tumor mass in the bronchus. At operation the mass had all the characteristics of a malignant lesion therefore the right lung was resected. Pathological examination revealed amyloid material forming a single tumor and causing obliteration of a bronchus of the right lung and collapse of the adjacent pulmonary tissue.

Primary amyloidosis affects the lungs either as a diffuse interstitial fibrosis spreading from the hilt into both organs or as a localized process involving one or both major bronchi simulating neoplasm. The latter picture was encountered in the case reported by Perla and Gross previously mentioned as well as in the following case recently reported by Schottenfeld and co workers from the same institution.

Case 7 Male—Age 43

Five years prior to admission to the Montefiore Hospital the patient noted weakness and shortness of breath. Later he developed cough and expectoration. On one occasion he was treated for pneumonia of the left lower lobe. The symptoms of dyspnea wheezing and productive cough recurred and he was once again hospitalized for suspected pneumonia this time of the right lower lobe. The patient had two additional episodes of pneumonia characterized by fever chills cough dyspnea and repeated hemoptysis prior to his present hospitalization.

On admission to the hospital the pertinent findings were limited to the lungs. The chest x-ray revealed a large irregular density extending from the left hilar region into the left middle and lower lung fields involving chiefly the lingula (Figures 9A and B). Bronchoscopy disclosed a lesion consisting of projecting masses extending in irregular fashion from the subglottic area down to the carina which was considerably broadened and further into both main bronchi. The bronchoscopist's original impression was an infiltrating carcinoma. However on histologic examination no tumor was found but amyloid deposits were noted in the submucosa of the trachea (Figures 9C and D). Further studies



Figure 9 (See legend on opposite page)

failed to disclose any evidence of generalized amyloid disease. Bence Jones proteinuria was absent, bone marrow studies were negative for myeloma.

During the following year the patient had twelve additional bronchoscopic treatments to remove obstructing masses. At first these were done weekly, later, at longer intervals. Microscopic examinations of many sections revealed amyloid deposition in the mucosal and submucosal portions of the wall. Following each bronchoscopic removal of tissue there were subjective and objective improvement

Metastatic Calcification of the Lungs

INTRODUCTION

This condition refers to a metabolic disorder in which lime salts are deposited in presumably normal tissues. Dystrophic calcification refers to a disturbance in which lime salts impregnate tissues previously the seat of tuberculosis, histoplasmosis, suppuration and other chronic diseases. A clear distinction between the two forms of calcification is not always possible since combinations have been found in some cases. Metastatic calcification affects most often the lungs, kidneys and stomach because the normal excretion of acid from these organs is associated with greater alkalinity of the tissue cells. The lowered concentration of hydrogen ions in the latter favors the precipitation of calcium and phosphorus from the serum. A similar mechanism is ascribed to the dystrophic form: the necrotic tissue is associated with increased alkalinity because of the lowered CO_2 tension thus favoring precipitation of calcium phosphate.

ETIOLOGY

The phenomenon of metastatic calcification has been known for a century Virchow having described the condition as early as 1855 Loeper for isolated case reports chiefly in journals devoted to the basic sciences little interest was paid to the disturbance until Mulligan in 1947

After 10 bronchoscopic treatments the patient could perform a day's work comfortably but he continued to have cough and bloody sputum. At the time the case was reported by the authors the patient had shown steady improvement and the chest x-rays had revealed a significant decrease in size of the pulmonary density. The patient went to a health resort where, after one bronchoscopic removal of amyloid tissue in a physician's office the patient began to bleed and shortly thereafter died.

made an exhaustive review of all previously reported cases. In recent years increasing numbers of reports have been appearing in clinical journals describing the condition in association with the following:

Chronic renal disease may be associated with sufficient destruction of kidney tissue to interfere with the excretion of phosphates. The accumulation of phosphate in the blood causes a temporary decrease in calcium which in turn provokes a compensatory hyperplasia of the parathyroids (secondary hyperparathyroidism). The resulting increased secretion of parathormone is soon followed by supersaturation of the serum with calcium and phosphorus ions, demineralization of the bone and the deposition of excess calcium in soft tissues. In the presence of chronic glomerulonephritis associated with a marked degree of nephrocalcinosis, the calcium deposits in the kidney may, on rare occasion, be visible in roentgenograms. Arons and co-workers draw attention to the fact that the calcium deposition in cases of chronic glomerulonephritis associated with nephrocalcinosis, is more marked in the renal cortex in contrast to other forms of calcification (vitamin D intoxication, sarcoidosis, hyperparathyroidism) in which the calcification is more marked in the medullary pyramids.

• Primary hyperparathyroidism may cause hyper

Figure 9 Case 7 Amyloidosis of bronchus

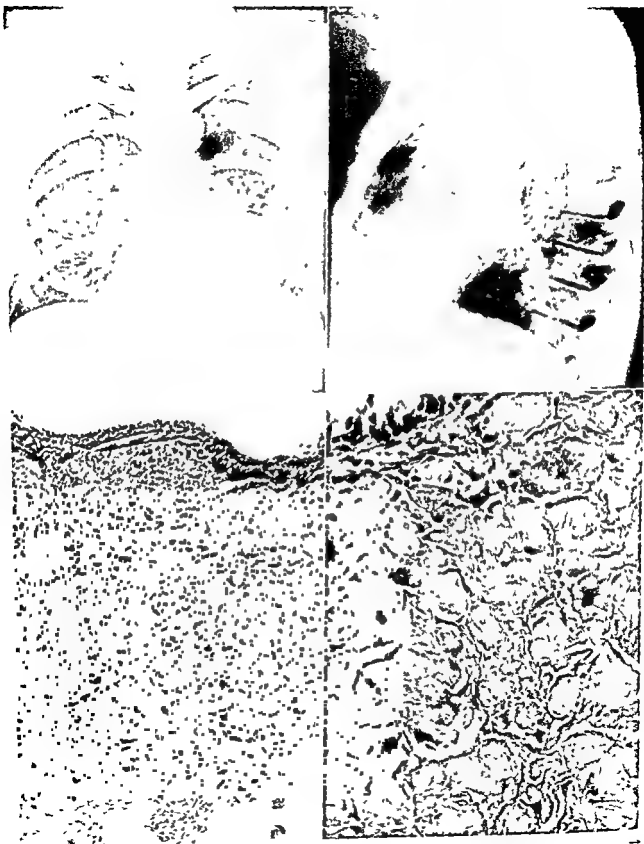


Figure 9 (See legend on opposite page)

failed to disclose any evidence of generalized amyloid disease. Bence Jones proteinuria was absent. Bone marrow studies were negative for myeloma.

During the following year the patient had twelve additional bronchoscopic treatments to remove obstructing masses. At first these were done weekly, later at longer intervals. Microscopic examinations of many sections revealed amyloid deposition in the mucosal and submucosal portions of the wall. Following each bronchoscopic removal of tissue there were subjective and objective improvement.

Metastatic Calcification of the Lungs

INTRODUCTION

This condition refers to a metabolic disorder in which lime salts are deposited in presumably normal tissues. Dystrophic calcification refers to a disturbance in which lime salts impregnate tissues previously the seat of tuberculosis, histoplasmosis, suppuration and other chronic diseases. A clear distinction between the two forms of calcification is not always possible since combinations have been found in some cases. Metastatic calcification affects most often the lungs, kidneys and stomach because the normal excretion of acid from these organs is associated with greater alkalinity of the tissue cells. The lowered concentration of hydrogen ions in the latter favors the precipitation of calcium and phosphorus from the serum. A similar mechanism is ascribed to the dystrophic form: the necrotic tissue is associated with increased alkalinity because of the lowered CO₂ tension thus favoring precipitation of calcium phosphate.

ETIOLOGY

The phenomenon of metastatic calcification has been known for a century. Virchow having described the condition as early as 1855. Except for isolated case reports chiefly in journals devoted to the basic sciences little interest was paid to the disturbance until Mulligan in 1947

After 10 bronchoscopic treatments the patient could perform a day's work comfortably but he continued to have cough and bloody sputum. At the time the case was reported by the authors the patient had shown steady improvement and the chest x-rays had revealed a significant decrease in size of the pulmonary density. The patient went to a health resort where after one bronchoscopic removal of amyloid tissue in a physician's office the patient began to bleed and shortly thereafter died.

made an exhaustive review of all previously reported cases. In recent years increasing numbers of reports have been appearing in clinical journals describing the condition in association with the following:

Chronic renal disease may be associated with sufficient destruction of kidney tissue to interfere with the excretion of phosphates. The accumulation of phosphate in the blood causes a temporary decrease in calcium which in turn provokes a compensatory hyperplasia of the parathyroids (secondary hyperparathyroidism). The resulting increased secretion of parathormone is soon followed by supersaturation of the serum with calcium and phosphorus ions, demineralization of the bone and the deposition of excess calcium in soft tissues. In the presence of chronic glomerulonephritis associated with a marked degree of nephrocalcinosis the calcium deposits in the kidney may on rare occasion be visible in roentgenograms. Arons and co-workers draw attention to the fact that the calcium deposition in cases of chronic glomerulonephritis associated with nephrocalcinosis is more marked in the renal cortex, in contrast to other forms of calcification (vitamin D intoxication, sarcoidosis, hyperparathyroidism) in which the calcification is more marked in the medullary pyramids.

Primary hyperparathyroidism may cause met

Figure 9. Case 7. Amyloidosis of bronchus. A (Upper left) Irregular density in left lower lung field increased hilar and bronchovascular markings in right lung. B (Upper right) Lateral projection shows density situated mainly at the hilum and in lingula. C (Lower left) Bronchus. Biopsy shows amyloid deposition through entire tunica propria (mucosa on top), bronchial gland (upper left corner). D (Lower right) Amorphous acellular hyaline amyloid in tunica propria (mucosa at upper left). (Repeated bronchoscopic removal of clots and amyloid masses followed by relief symptoms. Exsanguinating hemoptysis.) (From Schottenfeld, Arnold, Gruhn and Etes, *Am J Med* 11:770, 1951.)

astatic calcification. One is usually dealing with parathyroid neoplasms. Usually renal insufficiency is also present so that it may be difficult to distinguish the primary from the secondary varieties. Primary hyperparathyroidism is featured, in addition, by osteitis fibrosa cystica, localized giant cell tumors in the jaw and other bones and thyroid disturbances. Significant laboratory findings are an elevation of serum calcium, decrease in inorganic serum phosphorus and an increase in urinary output of calcium. However, the values may be within normal limits.

Sarcoidosis may be associated with metastatic calcification, nephrocalcinosis, nephrolithiasis and hypercalcemia. Davidson and co-workers reported seven cases of sarcoidosis with nephrocalcinosis. The calcifications occurred in the sarcoid lesions but for the most part were metastatic in nature since they were also found in other soft tissues including the lung in one case. In the particular instance, small discrete nodules of calcification were present in alveolar walls, some of which were thought to be within Schaumann bodies while others as linear metastatic calcifications. In another case, the question arose as to whether or not the pulmonary changes were actually those of a milary calcinosis. A similar case was reported by Schupbach and Wernly.

Davidson and co-workers found that hyperparathyroidism is a disease with which renal sarcoid is most likely to be confused. The differential diagnosis presented itself in two cases of a total of seven. Salmon and Meynell also described a case of hyperparathyroidism simulating sarcoidosis. Interestingly enough, the chest x-ray in their case showed coarse, diffuse striations in keeping with pulmonary sarcoidosis. After removal of the parathyroid adenoma, the lungs showed radiographic clearing. Other features in the differential diagnosis of sarcoidosis and hyperparathyroidism from a clinical standpoint are discussed in Chapter 9.

Destructive bone diseases, such as primary or metastatic sarcoma, metastatic carcinoma, multiple myeloma and osteomyelitis may be associated with metastatic calcification. Metastatic calcification may be present not only when there is obvious skeletal destruction but also in slow-

growing carcinomas of the breast, ovary and testicles without apparent bone involvement (Figure 10).

Excessive and prolonged use of highly potent vitamin D preparations (fortified cod liver oil or ultraviolet irradiated ergosterol, marketed under various trade names) is probably the most frequent cause of metastatic calcification. Wilson and co-workers refer to approximately 120 reported cases of this condition. Undoubtedly a greater number have not been reported. In a study of fifty-six cases of vitamin D intoxication from a single institution, Holman found eight in which pathologic calcification occurred. In addition to a history of prolonged ingestion of massive doses of high potency vitamin D preparations, there were clinical and laboratory evidence of renal insufficiency, an abnormally high concentration of phosphorus in the blood as well as the presence of rheumatoid or gouty arthritis.

Prolonged and excessive intake of absorbable alkali and milk may cause hypercalcemia and metastatic calcification without renal insufficiency. In the vast majority of cases the hypercalcemia is associated with renal insufficiency and azotemia. In a collected series of twenty-one cases, including three of his own, Kessler found that the patients had ingested both milk and absorbable alkali, in the exception only absorbable alkali. In spite of withdrawal of absorbable alkali and low calcium diet the treatment had no bearing on the outcome although improved renal function was obtained in many.

PATHOLOGY

As mentioned, the lungs are among the most frequent organs involved in metastatic calcification. In Mulligan's collected series, the lungs were affected in thirty of thirty-five cases with bone disease, in twelve of twenty-three cases with chronic renal disease (renal rickets), in twelve of twenty-one cases with primary parathyroid neoplasms and in three of nine cases with hypervitaminosis D.

Gross examination of lungs, which are the seat of metastatic calcification, may give little visible evidence of the extent of changes present within the organs even when disease is evident in other

parts of the body. The lungs may have a 'normal' appearance or show only moderate emphysema. In the presence of long standing disease, the organs are usually firm, tough and gritty with a network of linear streaks outlining the alveolar septa. The histologic appearance of the lung as seen in a number of cases studied at the Montefiore Hospital, is characterized by the presence of minute calcific foci in the form of plates and rods impregnating the alveolar septa, also spicules of calcium, often with giant cell formation, in the interstitial fibrous tissue. Calcification is seen in the walls of many of the capillaries, small blood vessels, also in the capillaries of bronchioles and in the bronchi themselves. In calcifying metastatic carcinoma, calcified masses impregnate the neoplastic deposits.

ROENTGENOLOGY

In spite of the high incidence of pulmonary involvement, metastatic calcification of the lungs is rarely recognized during life except in in-

stances of calcifying, malignant neoplasms with pulmonary metastases. In one of the cases, reported by Burnett and co workers, the calcification was sufficiently prominent to outline the bronchi in the chest x-ray. The systemic nature of the disease is evident in the demineralization of long bones, diffuse calcinosis in soft tissues, especially around rheumatoid joints, and the calcified masses demonstrable roentgenologically in the abdomen, in the region of the kidneys.

The failure to recognize metastatic calcification of the lungs during life is due in part to the widely scattered calcific foci in the finer architecture of the parenchyma. Yet, this is probably not the major cause since similarly dispersed calcific foci are readily discernible in tuberculosis, histoplasmosis and other diseases. The difficulty of diagnosis of lung lesions probably lies in the fact that metastatic calcification is usually diagnosed in the late stages of its development and any abnormal markings in the chest x-rays are apt to be ascribed to associated cardiorenal compli-

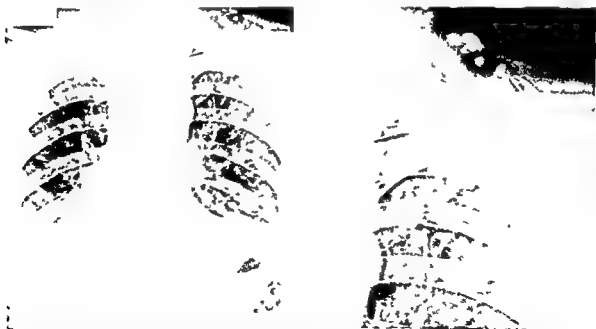


Figure 10. Calcifying carcinoma of breast with calcific metastatic deposits in lungs and lymph nodes. A (Left) Calcific foci in left upper lobe and left supraclavicular lymph nodes; several foci faintly seen in right upper lobe and above right clavicle; fracture of second left rib, anteriorly; upward displacement of left leaf of diaphragm (due to phrenic nerve involvement). B (Right) Lung detail (Seven years previously patient had a left radical mastectomy for carcinoma; histologic examination of tumor revealed calcifying carcinoma; biopsy of supraclavicular lymph node also showed calcifying carcinoma).

cations which almost invariably coexist. But if one inspects overexposed chest films or Buckley films of patients with metastatic calcification, one may be able to delineate within the visible lung

fields a reticular, granular network of infiltrations or possibly calcific plaques in bronchi in keeping with the underlying disease.

Bibliography

HISTIOCYTOSIS WITH PULMONARY INVOLVEMENT

- BIERNAN, H. R., LANNAN, J. T., DOD, K. S., KELLY, K. H., MILLER, E. R. and SHIMKIN, M. B. The Ameliorative Effect of Antibiotics on Nonlipid Reticuloendotheliosis (Letterer-Siwe Disease) in Identical Twins. *J. Pediatr.* 40: 769, 1952.
- BODIAN, M. Survey of the Pathological Features of Hand-Schüller-Christian Syndrome, Letterer-Siwe Disease and Eosinophilic Granuloma of Bone. *Proc. Royal Soc. Med.* 48: 713, 1955.
- CHESTEN, W. and KUCIEL, V. B. Lipoid granulomatosis (Type Hand-Schüller-Christian). *Arch. Path.* 14: 595, 1952.
- CHILDS, D. S. JR. and KENNEDY, R. L. J. Reticuloendotheliosis of Children. Treatment with Roentgen Rays. *Radiology* 57: 653, 1951.
- CLAIREAUX, A. E. and LEWIS, I. C. Reticuloendothelial Granuloma. A Review with Report of a Case of Letterer-Siwe Disease. *Arch. Dis. Child.* 25: 147, 1950.
- CURRENS, J. H. and POPP, W. C. Xanthomatosis (Hand-Schüller-Christian Type). Report of a Case with Pulmonary Fibrosis. *Am. J. Med. Sc.* 205: 780, 1943.
- DAVIS, E. W. Discussion on The Etiology of Chronic Interstitial Pneumonitis Associated with Lipid Deposition by Waddell et al. *J. Thoracic Surg.* 28: 147, 1954.
- DE NAVASQUEZ, S. and HASTENWOOD, G. A. D. Endogenous Lipid Pneumonia with Special Reference to Carcinoma of the Lung. *Thorax* 9: 35, 1954.
- DENNIS, J. W. and ROYAN, P. D. The Primary Reticuloendothelial Granulomas. With Report of an Atypical Case of Letterer-Siwe's Disease. *Am. J. Path.* 27: 67, 1950.
- FORBES, J. H. and BLAKE, H. A. Pulmonary Cystic Changes in Xanthomatosis. *Ann. Surg.* 139: 76, 1954.
- FRETZ, W. I. Diabetes Insipidus and Pulmonary Fibrosis. *Arch. Int. Med.* 95: 873, 1955.
- GOODRICH, V. Histiocytic Granuloma of Skull (Triphasic Clinico-Pathologic Syndrome Previously Termed Letterer-Siwe's Disease, Hand-Schüller-Christian's Disease and Eosinophilic Granuloma). *Laryngoscope* 60: 1, 1950.
- GRANT, L. J. and GINSBURG, J. Eosinophilic Granuloma (Honeycomb Lung) with Diabetes Insipidus. *Lancet* 2: 579, 1954.
- GROSS, P. and JACOB, H. W. Eosinophilic Granuloma and Certain Other Reticuloendothelial Hyperplasias of Bone. *Am. J. Med. Sc.* 203: 673, 1947.
- HANSEN, P. B. The Relationship of Hand-Schüller-Christian's Disease, Letterer-Siwe's Disease and Eosinophilic Granuloma of Bone. *Acta Radiol.* 32: 89, 1949.
- HOBSON, J. R., KENNEDY, R. L. J. and CAMP, J. D. Reticuloendotheliosis. *Radiology* 57: 647, 1951.
- JAFFE, H. L. and LICHTENSTEIN, I. Eosinophilic Granuloma of Bone. A Condition Affecting One Several or Many Bones but Apparently Limited to the Skeleton and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis Also Underlying Letterer-Siwe Disease and Schüller-Christian Disease. *Arch. Path.* 37: 99, 1944.
- KARGER, G. O. JR., PRICKMAN, L. C., and PUGH, D. G. So-called Eosinophilic Granuloma of the Ribs and Jaws Associated with Visceral (Pulmonary) Involvement Characteristic of Xanthomatosis. *Oral Surg. Oral Med. and Oral Path.* 2: 770, 1949.
- LACKEY, R. W., LEAVER, F. Y., and FARINACCI, C. J. Eosinophilic Granuloma of the Lung. *Radiology*, 59: 504, 1952.
- LICHTENSTEIN, I. Histiocytosis. An Integration of Eosinophilic Granuloma of Bone, Letterer-Siwe Disease and Schüller-Christian Disease as Related Manifestations of a Single Nosologic Entity. *Arch. Path.* 56: 84, 1953.
- LICHTENSTEIN, I. and JAFFE, H. L. Eosinophilic Granuloma of Bone with Report of Case. *Am. J. Path.* 16: 595, 1940.
- LIGHTWOOD, R. Histiocytic Type of Reticuloendotheliosis. *Proc. Royal Soc. Med.* 48: 711, 1955.
- LIGHTWOOD, R. and TIZARD, J. P. M. Recovery from Acute Infantile Nonlipid Reticuloendotheliosis (? Letterer-Siwe Disease). *Acta paediatr., suppl.* 43: 453, 1954.
- MACDONALD, A. M. and SHANKS, R. A. Honeycomb Lung and Xanthomatosis. *Arch. Dis. Childhood*, 29: 127, 1954.
- MAZZITELLO, W. F. Eosinophilic Granuloma of the Lung. *New England J. Med.* 250: 804, 1954.
- MEBOFF, A. S. and BAYRD, E. D. Gaucher's Disease in 29 Cases. Hematologic Complications and Effect of Splenectomy. *Ann. Int. Med.* 40: 481, 1954.
- MYERS, B. Gaucher's Disease of the Lungs. *Brit. M. J.* 2: 8, 1937.
- ORCHARD, N. P. Letterer-Siwe's Syndrome. Report of a Case with Unusual Peripheral Blood Changes. *Arch. Dis. Childhood* 25: 151, 1950.
- OSWALD, M. and PARKINSON, T. Honeycomb Lungs. *Quart. J. Med.* 18: 1, 1949.
- OTANI, S. and EHREICH, J. Solitary Granuloma of Bone Simulating Primary Neoplasm. *Am. J. Path.* 16: 49, 1940.
- PARKINSON, T. Eosinophilic Xanthomatous Granuloma with Honeycomb Lungs. *Brit. M. J.* 1: 1079, 1949.
- PHILLIPS, F. W. Intrathoracic Xanthomatous Neoplasms. Report of Two Cases and the Collection of Three Similar Cases in the Literature. *J. Thoracic Surg.* 7: 74, 1937.
- PINKUS, H., COPPEL, L. A., CUSTER, S. and LESTER, S. Reticuloendothelial Granuloma. Report of a Case of Eosinophilic Granuloma of Bone Associated with Nonlipid Reticulosis of Skin and Oral Mucosa Under the Clinical Picture of Hand-Schüller-Christian Disease. *Am. J. Dis. Child.* 70: 503, 1949.
- ROBBINS, L. L. and SNIFFEN, R. C. Correlation Between the Roentgenological and Pathologic Findings in Chronic Pneumonitis of the Cholesterol Type. *Radiology* 53: 187, 1949.

DISEASES OF METABOLISM (CONCLUDED)

51

- RAVEN E H *Diseases of the Chest* Philadelphia W B Saunders Company 1947 p 437
- STENGER E L and JOHNSON R J Letterer Weiss Disease Problems in Diagnosis and Treatment *Am J Roentgenol* 71:47 1954
- SCHNEIDERMAN S J and SCHNEIDER L Lipoid Granulomas (Xanthomas) with Marked Pulmonary Fibrosis and Cor Pulmonale As Outstanding Manifestations *Ann Int Med* 30:84 1949
- SCOTT H W Jr MORRIS A G and PAIN T P B Solitary Anthoma of the Lung *J Thorac Surg* 17:81 1948
- SPILLANE J D Four Cases of Diatheses Infiltrative and Pulmonary Disease *Thorax* 7:114 1952
- STRALS B Metabolic and Inflammatory Histologic With Case Reports of Gaucher's Disease Letterer Weiss Disease and Eosinophilic Granuloma *Am J Med* 5:245 1948
- TERRY R D SPERRY W M and BRONOFF B Adult Lipidosis Resembling Niemann-Pick's Disease *Am J Pathol* 63:1954
- THANHAUSER S J and MAGENDAN H The Different Clinical Groups of Xanthomatous Diseases A Clinical Physiologic Study of 11 Cases *Ann Int Med* 11:167 1938
- TROVIER E R and WEINSTEIN D Generalized Xanthomatosis with Pulmonary Skeletal and Cerebral Manifestations *Ann Int Med* 75:960 1946
- WADSWORTH W R SWIFT R C and WYTHIAN L L The Etiology of Chronic Interstitial Pneumonia Associated with Lipid Deposition *J Thorac Surg* 78:134 1954
- WALLGREN A Systemic Reticuloendothelial Granuloma *Am J Dis Child* 60:471 1940
- REIMANN H A SUTOW P G and CHACALIAN H T Primary Amyloidosis *Arch Int Med* 93:673 1954
- SAPPINGTON S W DAVIS J H and HORVATH J A Primary Amyloidosis of the Lungs *J Lab & Clin Med* 27:487 1947
- S HOTTENFELD A ARNOED L M GRUEN J G and EDESS A D Localized Amyloid Deposition in the Lower Respiratory Tract *Am J Med* 11:770 1951
- WEISSMAN R E CLARKE O T and McDONALD J R Amyloid Disease of the Lung Treated by Pneumectomy *J Thorac Surg* 16:759 1947
- WINTERL F Localized Amyloid Infiltrations of the Lower Respiratory Tract *Thorax* 8:309 1953

METASTATIC CALCIFICATIONS OF THE LUNGS

- ARONS W L CHRISTENSEN W R and SCHWARTZ M C Nephrocalcinosis Visible by X-Ray Associated with Chronic Glomerulonephritis *Ann Int Med* 42:260 1955
- BLANETT C H COMBES R B ALBRIGHT F and HONARD J S Hypercalcemia Without Hypercalcemia or Hypophosphatemia Calciosis and Renal Insufficiency *New England J Med* 240:87 1949
- DANFORTH C A DENNIS J M MCNICH E R WILSON J K A and BOGGS W H Nephrocalcinosis Associated with Sarcoidosis *Radiology* 67:701 1954
- HOLMAN C B Roentgenologic Manifestations of Vitamin D Intoxication *Radiology* 59:805 1952
- JAFFE H L Primary and Secondary (Renal) Hyperparathyroidism *S Clin North America* 22:61 1947
- KARR W J in discussion on FARRINGTON R H GRANT R and ROSS M A Hypoparathyroidism Treatment of Chronic Cases *J A M A* 107:169 1936
- KESLER E Hypercalcemia and Renal Insufficiency Secondary to Excessive Milk and Alkali Intake *Ann Int Med* 47:374 1955
- MILLER R M Metastatic Calcification *Arch Pathol* 41:1 1947
- NATHANSON L Calcified Metastatic Deposits in the Peritoneal Cavity Inner and Outer Field from Papillary Carcinoma of the Ovary *Am J Roentgenol* 64:46 1954
- JOHNSON H W and MEYER G C Primary Hyperparathyroidism (Adenoma) Stimulating Sarcoidosis *Bull N Y Acad Med* 2:1440 1951
- SCHLIMM A and FERNEL M Hypercalcemia und Organverfaltungen bei Boeck'scher Krankheit *Acta med scandin* 117:401 1943
- WEINER P KESNER M and RILEY F A Reversible Metastatic Calcification Associated with Excessive Milk and Alkali Intake *Am J Med* 14:108 1953
- WILSON C W WINFIELD W L and THOMPSON F C Jr Vitamin D Poisoning with Metastatic Calcification *Am J Med* 14:116 1953
- DAHLIN D C Primary Amyloidosis With a Report of Six Cases *Am J Pathol* 27:105 1947
- DURAN P R Primary Amyloidosis of the Lungs *Am J Roentgenol* 56:777 1946
- HANSEN A L CLARKE O F and McDONALD J R Immune Forming Amyloidosis of the Lung *Surgery* 24:170 1948
- HIGGINS W H and HIGGINS H H Jr Primary Amyloidosis *Am J Med* 7:610 1950
- LEWIS O Zur Kenntnis ungewöhnlicher Amyloidbildungen *Arch Pathol Anat* 77:88 1949
- MAHMOUD W H Primary Systemic Amyloidosis *Am J Med* 77:317 1954
- PARL D and GROSS H Atypical Amyloid Disease *Am J Pathol* 11:93 1955
- REIMANN H A KOLCH R F and LITMAN C M Primary Amyloidosis Limited to Tissue of Mesodermal Origin *Am J Pathol* 11:9 1955

Diseases of the Blood

Introduction

DISEASES OF THE BLOOD and blood forming organs seldom affect the lungs. Occasionally, sickle cell anemia and hemosiderosis rarely polycythemia vera and hemorrhagic dyscrasias are associated with pulmonary lesions. The leukemias often involve the intrathoracic lymph nodes but not the lung parenchyma to an extent that the disease is demonstrable roentgenologically. Infectious mononucleosis although featured by hematological findings is not strictly speaking a blood disorder being most likely caused by a

virus. The disease will be included in this chapter simply to round out the discussion of the subject. Pernicious anemia does not involve the lungs directly but it does exert a deleterious effect on any superimposed bacterial or viral infection. The frequent association of secondary anemia and diaphragmatic hernia is well recognized and need only be mentioned. The loss of blood in this condition is not necessarily related to the amount of gastrointestinal bleeding.

Pulmonary Diseases Associated with Unusual Blood Findings

Before elaborating on the pulmonary manifestations of blood diseases it is not out of order to discuss the reverse of the picture—pulmonary diseases which may be associated with unusual blood findings.

TUBERCULOSIS

The simultaneous occurrence of leukemia and tuberculosis has been noted on many occasions. The presence of one disease need not influence the course of the other. At times a dormant tuberculosis may become activated by a superimposed leukemia or else an existing leukemia may become suppressed with the appearance of acute tuberculosis. In many cases it is difficult to establish an exact chronological let alone causal relationship between one disease and the other. Some of the older writers speculated that tuberculosis may be a cause of leukemia. The majority now advise believe that the blood changes are of leukemoid nature rather than a true leukemia. Difficulties in differential diagnosis often arise when a leukemoid blood picture is present but a

definition of the latter may not be easy. Hill and Duncan consider as leukemoid any reactions in which the following are found: (a) a total leukocyte count over 50,000; (b) the presence of immature cells of the blast type; or (c) a combination of (a) and (b). A third prerequisite offered by Heck and Hall, is that if autopsy the organs and tissues should show no leukemic changes.

Leukemoid reactions of the granulocytic (myeloid) type are encountered in acute generalized hematogenous tuberculosis. Leibowitz reported the case of a twenty-nine-year-old white female who had evidence of tuberculosis of both upper lobes and spine and who developed an acute activation of the disease featured by a myeloblastic blood picture. Because of the severity of the illness, profound anemia, lesions of the mouth, purpuric spots, high fever and hepato-splenomegaly, the diagnosis was that of an acute myelogenous leukemia until the postmortem examination revealed that the patient had died of a tuberculous septicemia with widespread caseo-

necrotic foci containing masses of acid fast organisms. Leibowitz refers to several cases reported by others in which acute forms of hematogenous tuberculosis were associated with bizarre blood pictures.

A case was recently discussed at a clinical pathological conference by Kuzma and others in which a sixty four year old patient developed symptoms and signs in keeping with a right lower lobe pneumonia. The hematological findings were featured by anemia, leucopenia and thrombocytopenia. The patient died and at autopsy the liver, spleen, kidney and lymph nodes showed caseous tuberculous abscesses containing large numbers of tubercle bacilli. The lesions were of a soft variety with very little tissue reaction in the way of giant cells, fibrosis or lymphocytosis. Hendry found that tuberculosis when associated with thrombocytopenia is almost invariably a disseminated disease. In such cases it is presumed that the bone marrow involvement is the factor responsible for the onset of the purpura. In a small number of tuberculosis cases thrombocytopenic purpura. When thrombocytopenic purpura occurs in other forms of tuberculosis the association is merely coincidental.

From an experience with a sizable number of patients with generalized hematogenous tuberculosis I am impressed with the much more frequent occurrence of an absolute or relative leucopenia and a relatively high lymphocytic count rather than a leukemoid picture. Leucopenia is apt to be encountered in hematogenous tuberculosis affecting the abdominal organs especially the spleen. The abdominal distress, vomiting, fever and prostration a relatively low pulse leucopenia and an enlarged spleen even a rash in the skin characterize the so called typhoid form of hematogenous tuberculosis (Landouzy).

On rare occasion tuberculosis may be associated with polycythemia. This combination is more apt to occur in patients with chronic recurrent hematogenous tuberculosis in which the spleen is the major seat of involvement. I have met with two patients in whom the presence of an enlarged spleen led to a mistaken diagnosis of Banti's disease. Cases are also on record of acute generalized hematogenous as well as

chronic caseous cavernous tuberculosis occurring in association with polycythemia. But it is not always easy to determine whether or not one is dealing with polycythemia vera or polycythemia occurring in response to increased oxygen demand. On rare occasion as pointed out by Fountain generalized hematogenous tuberculosis may be associated with profound depression of the matopoieses resulting in pancytopenia and a picture in keeping with aplastic anemia.

MALIGNANT NEOPLASMS

Leukemoid reactions may be encountered in association with malignant neoplasms including those of the lungs. As a rule the malignancy is in an advanced stage and skeletal metastases are present. Fahey reported leukemoid reactions in three of 160 cases of carcinoma of the lung. Similar experiences have been cited by others. In a case reported by Henkin bone metastases became visible roentgenologically five months after the height of the leukemoid reaction. In a patient recently exhumed at autopsy at Montefiore Hospital there was found a bronchiogenic carcinoma with widespread bone and visceral metastases. There was a coexisting chronic lymphocytic (lymphatic) leukemia (WBC 56 000 to 101 000 lymphocytes 80 per cent) affecting the bone marrow, spleen and liver. The symptoms referable to the pulmonary disease and the recognition of the leukemia occurred within one month of each other.

Among the various causes of eosinophilia malignancy is also occasionally mentioned. Isaacson and Rapoport described fifteen cases of eosinophilia in a review of 2 363 cases of malignancy. The authors found nineteen additional cases reported in the literature including two instances of bronchiogenic carcinoma with widespread metastases. Attention is drawn to the fact that in 90 per cent of the cases metastases were present and that in an additional 7 per cent metastases were suspected but not proved. In the instance of bronchiogenic carcinoma described by these authors the metastases were so widespread and the leukemoid reaction and eosinophilia so pronounced that a diagnosis of eosinophilic leukemia was made clinically.

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

Malignant pulmonary neoplasms may also be complicated by hemolytic anemia. The type of anemia encountered has been designated by Singer and Dimeshek, as the symptomatic hemolytic variety. A rare instance of a large anterior mediastinal tumor complicated by aplastic anemia is reported by Humphreys and Southworth. A woman, aged fifty eight, had been treated for almost two years with repeated blood transfusions without effect. After removal of the tumor, which histologically appeared to be probably thymic in origin, there was a sharp rise in reticulocytosis and the erythrocyte count returned to normal range. The patient died one year after the operation. Autopsy revealed many deposits of iron pigment in the tissues. It was suspected that death was caused by liver insufficiency secondary to advanced hemochromatosis due to the long course of transfusions. The authors refer to another instance, reported by Opsahl, of thymic carcinoma complicated by aplastic anemia.

Although not directly bearing on the subject it might be interesting to mention a case recently observed at the Montefiore Hospital. A fifty-year old woman had been suspected of having primary tuberculosis. The illness had lasted about four months, the symptoms and signs for a time pointed to a viral infection. The initial chest x rays revealed no lesions, but subsequent x rays revealed increasing crops of miliary foci seeding both lungs. The patient developed ecchymoses over the thighs. A blood examination by Dr S Melamed revealed a thrombocytopenia of an aplastic variety (platelet counts ranged from 50,000 to 75,000). In spite of repeated blood transfusions the patient died. The autopsy revealed a primary adenocarcinoma of the ascending colon and widespread metastases to the lungs, lymph nodes and bones. Cone and Nayer reported a case of thrombocytopenic purpura complicating primary bronchiogenic carcinoma. The blood findings indicated metastatic involvement.

Sickle Cell Anemia

In 1910 Herrick described a case of severe anemia characterized by peculiar elongated sickle shaped red blood corpuscles. Since the publication of this report, sickle cell anemia has become recognized as a primary, hereditary, blood dyscrasia affecting Negroes almost exclusively. It is estimated that the sickle cell trait (sicklelema), in the absence of the specific hemolytic anemia, occurs in from 7 to 8 per cent of Negroes in the United States. The ratio of sickle cell anemia to the sickle cell trait is about one to forty. In acute sickle cell anemia the elongated multipointed erythrocytes interlock and obstruct the capillaries, the resulting stagnation of blood causing congestion, thrombosis and infarction of the affected parts. The accompanying destruction of erythrocytes gives rise to varying degrees of hemolytic anemia. Although the major pathological changes are found in the bone marrow, skeletal system and spleen the disease may affect any organ. The most pronounced cell crises which recur from time to time and are characterized by fever and pain in the abdomen, thorax and joints. Additional signs are jaundice,

lymphadenopathy, cardiac enlargement, ulcers of extremities, hemorrhagic tendencies and respiratory infections.

The pulmonary manifestations of sickle cell anemia have received comparatively little study, although respiratory tract infections are common, often precipitating crises and frequently causing death. In a study of fifty four cases of sickle cell anemia, Henderson found pneumonia as a presenting sign in fourteen. In a similar study of thirty-seven children, Scott and co-workers found twelve with roentgen evidence of pulmonary congestion or consolidation. In a review of seventeen consecutive cases of sickle cell anemia treated at the Morrisania City Hospital, I found only three instances in which the chest x rays failed to reveal some type of abnormality. Many of the patients had been hospitalized repeatedly during recurring crises or for treatment of intercurrent complications. Pregnancy is a particularly serious hazard to the mother as well as to the fetus.

The pathological changes in the lungs are characterized by capillary stasis, a tendency to thrombus formation and infarction. Roentgeno-

logically one meets with a variegated picture, a normal chest x ray being seldom seen. There is a constant lability in the roentgen changes. Marked variations are noted in the size and configuration of the cardiac silhouette. The pulmonary markings range the gamut from increased bronchovascular shadows to irregular patchy infiltrations in the mid and lower portions of the lungs or massive consolidations. After frequent transfusions one may encounter a soft veil like haziness over both lung fields. On rare occasion one finds nodular densities symmetrically distributed in both lungs in keeping with hemosiderosis or minute infarctions. The evanescent nature of the roentgen changes usually preclude exact definition of the nature of the pulmonary lesions. In many instances the findings are in keeping with pulmonary congestive changes possibly associated with pulmonary infarction.

Case 8 Female Negro—Age 31

Admitted to the obstetrical service of the Morrisania City Hospital on July 27, 1949 in acute respiratory distress and generalized edema which had been getting progressively worse during the preceding week. During the twenty four hours prior to her admission to the hospital the patient had not felt fetal movement. The patient had made one prenatal visit three months previously and subsequently had attended the cardiac clinic for suspected heart disease. The patient had three normal spontaneous deliveries in 1937, 1939 and 1947. In 1940 she had a stillborn breech delivery. Following that delivery she had a seizure of respiratory distress and was given a blood transfusion. Since childhood the patient had joint pains and unexplained anemia which were ascribed to rheumatic fever.

Physical examination revealed a critically ill woman markedly dyspneic and orthopneic. The fetal heart sounds were not heard. There was moderate edema of the abdominal wall and marked edema of the lower extremities. The hemoglobin was 15 gms. red blood cells 5,800,000, white blood cells 31,000. The reticulocyte count was 16 per cent. The urine showed 3 plus albumin and was positive for bile and urobilinogen. External marrow smears showed a hyperactive bone marrow. A sickle cell preparation at 10 hours showed 95 per cent sickling. The patient was placed under oxygen and given repeated blood transfusions. She soon began to complain of severe

abdominal pain for which she received sedatives and demoral. Two days after admission she had a chills progressive rise in temperature and the patient was started on penicillin. A chest x ray at this time revealed diffuse infiltrations in both lungs with an irregular triangular area of density in the right midlung field with accentuation of the small fissure also obscuration of both costophrenic sinuses. The cardiac shadow was enlarged and the pulmonary conus prominent. Both leaves of the diaphragm were displaced upward (Figure 11A).

The following day the patient went into spontaneous labor and after one hour delivered a seven pounds 7 ounces stillborn macerated infant. The uterus contracted well and there was a normal amount of blood loss. Immediately after delivery the temperature rose to 103.4° the hemoglobin was 6 gms. Blood transfusions were continued. On the third day postpartum the temperature returned to normal. The blood picture showed progressive improvement and the patient was discharged to the clinic on the tenth postpartum day. A late follow up chest x ray showed almost complete disappearance of the infiltrations in both lungs.

As might be expected tuberculosis is another serious complication frequently encountered in patients with sickle cell anemia. Weiss and Waife found that Negroes with sickle cell anemia show a higher incidence of pleuropulmonary inflammatory disease as evidenced by a higher incidence of pleural adhesions and a higher incidence of various forms of tuberculosis than do Negroes without sickle cell anemia. Weiss and Stecher also found that the sickling trait is more than twice as common (12.6 per cent) among tuberculous Negroes admitted to the Philadelphia General Hospital as among non tuberculous Negroes admitted to the same hospital (5.3 per cent). In their study, exudative tuberculosis was found twice as common among tuberculous Negroes with the sickling trait (74 per cent) as among tuberculous Negroes without the trait (38 per cent). The authors concluded that the sickling trait has a definite clinical significance and is a factor in the response of some Negroes to tuberculous infection. The findings of Weiss and co workers have not been confirmed by

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE



Figure 11 Case 8 Sickle cell anemia with pulmonary involvement. Changes in both lungs especially the midportions and bases heart enlarged diaphragm displaced upward B (Left) enlarged heart anemia consolidation in a woman with

A (Upper) Marked consolidation areas of consolidation at considerable clearing of in acute respiratory syndrome)

Rosenblum and co workers who found that neither the extent of the pulmonary tuberculosis nor the age at which it first became clinically evident was influenced by the coexistence of the sickle cell trait

It might be interesting to cite an experience with a Negro girl with sickle cell anemia who was under my observation for a number of years and who presented an unusual course of events. The patient was first admitted to the Morrisania City Hospital at the age of fourteen with advanced ciseocarcinoma tuberculosis of the left upper lobe. She had been treated previously at the hospital on various occasions for recurrent sickle cell crises. After the diagnosis of tuberculosis was made a left sided pneumothorax was

induced and the treatment continued at the Seron Hospital. In time the patient developed a pleural effusion and the pneumothorax had to be abandoned. When streptomycin became available she received the antibiotic for two months and eventually the disease became arrested. At the age of nineteen she became pregnant and delivered a live infant. This young Negro girl with sickle cell anemia was able to overcome an advanced tuberculosis and to go through pregnancy successfully—accomplishments worth citing. It might be pertinent to add that since the introduction of potent antibacterial agents the lives of many patients with sickle cell anemia have been materially prolonged.

Pulmonary Hemosiderosis

Focal deposits of iron particles in the lungs may arise from exogenous as well as endogenous sources. Exogenous siderosis may be due to inhalation of dusts or fumes in occupations in which ferrous metals are used. The disease is encountered among metal grinders, arc welders and silver finishers. Endogenous siderosis (hemosiderosis) is a non occupational disease occurring in association with long standing mitral stenosis, advanced left ventricular failure following repeated blood transfusions in certain forms of malnutrition encountered in South African Negroes and as a result of excessive parenteral administration of iron. Pulmonary hemosiderosis may also occur without apparent cause. The latter form is known as idiopathic hemosiderosis.

An attempt to correlate the pathological findings with the clinical state and catheter studies of individual patients. Of particular interest were the high degree of parallelism between the extent of hemosiderosis present in the histological sections and the amount of roentgenological mottling. The roentgenological assessment was made according to a scale graded from 3 to 0 depending on the degree of mottling. The latter was compared with a histological scale based on the density of siderophores and the total number of foci seen in the sections. The authors found that hemosiderosis was almost universal in patients showing the clinical effects of mitral stenosis and that there was a reasonable correlation between the individual assessment of hemosiderosis from the roentgenological appearance and the histological findings at lingular biopsy.

IN ASSOCIATION WITH MITRAL STENOSIS

Until recently the association of hemosiderosis and mitral stenosis was considered a rarity, as attested by the occasional reports describing single cases. Lately there has been an increasing awareness of this condition as a result of more frequent chest roentgenography. A valuable contribution to the subject was made by Enticknap and co workers who reported findings on lingular biopsies obtained from forty patients who had mitral valvulotomy. The biopsies were done in

Analogous observations were reported by Lendrum and co workers. These investigators found focal hemosiderin deposits of various degrees in every instance of twenty six cases of mitral stenosis in which abnormalities of the tricuspid valve were slight or absent. These authors likewise concluded that hemosiderosis apparently occurs in every case of mitral stenosis associated with right ventricular hypertrophy. The authors failed to find hemosiderosis in the absence of right ventricular hypertrophy because of an as

sociated tricuspid stenosis or other factors Taylor and Strong found focal accumulation of hemosiderin containing phagocytes forming distinct nodules in the lungs in 47 per cent of cases dying with advanced mitral stenosis. In an additional 31 per cent the lungs presented the more classic finding of brown induration i.e. diffuse siderophages without distinct focal collections. Esposito reported a somewhat lower incidence of hemosiderosis in rheumatic heart disease. Of 100 patients examined at autopsy twenty eight showed histopathological changes being more pronounced in advanced disease.

The mechanism of hemosiderosis in patients with mitral stenosis is readily understandable. The engorgement of the pulmonary capillaries incident to the hypertension of the lesser circulation caused by the stenotic mitral valve gives rise to recurring minute hemorrhages in the air spaces. After hemolysis of the extravasated red cells the liberated iron free fraction (hemaetin) is absorbed the iron containing fraction (hemosiderin) remains in the tissues and initiates a foreign body reaction. The minute dark brown spots often visible grossly in the visceral pleura and readily on histological examination of the tissues consist of irregularly distributed nodules within the lung alveoli and in the adjacent stroma (Figures 12C and D). The nodules represent deposits of hemosiderin at times accompanied by fibrous proliferation of the alveoli. There may be an associated giant cell reaction occasionally calcification and on rare occasion ossification. However Taylor and Strong believe that the small calcified or bony nodules are distinct from and unrelated to the aggregates of siderophages which do not contain any stainable calcium. They believe it more likely that the bony and calcific nodules are the end result of rheumatic pneumonia organized thrombi or other pathologic lesions. Kent and associates reported a case of pulmonary microlithiasis and referred to four teen additional cases reported in the literature. This rare disease is caused by the deposition of innumerable minute intraalveolar calculi throughout the lungs. The calculi resemble morphologically corpora amylacea and the condition has been described under the latter head

ing. Noteworthy is the fact that among the agents which might be responsible mitral stenosis is mentioned by several observers.

Pulmonary hemosiderosis associated with mitral stenosis manifests itself roentgenologically in fine nodular densities diffusely scattered throughout both lungs but most numerous in the midportions (Figure 12A and B). According to Lendrum and associates the concentration of nodules in the midlung regions is due to the superimposition of tiny radiopaque nodules in the traversed lung. Depending on the thickness of the lung these nodules appear more numerous in the central portions and fade away toward the periphery. The nodules resemble those of military tuberculosis welders siderosis fine nodular forms of pneumoconiosis and histoplasmosis. There is usually little interstitial reaction between individual nodules. On rare occasion the nodulations are limited to a portion of a lung and the significance of such dispersions is easily overlooked unless one bears hemosiderosis in mind. This applies also to instances in which the roentgenological mottling is indefinite or not easily distinguishable from normal vascular markings. In any event in the presence of mitral stenosis and hypertension of the lesser circulation such mottlings are almost invariably due to hemosiderosis. At one time they were erroneously ascribed to military lung stasis congestion of the lungs or blood vessels caught on end. I have followed the course of events in a man of twenty seven who had rheumatic mitral disease since childhood. The minute nodules seen initially and simulating military tuberculosis gave way in time to a fine interstitial striation. The military foci were discovered in the course of a preinduction chest x ray examination. During the past twelve years the patient has remained well and at work.

✓ IDIOPATHIC PULMONARY HEMOSIDEROSIS

This condition first described by Ceelen in 1931 is encountered chiefly in infancy and childhood but at least four cases have been reported in ages ranging from sixteen to thirty eight (Tait and Corridan). In 1948 Wylie and co workers described seven cases and summarized seventeen

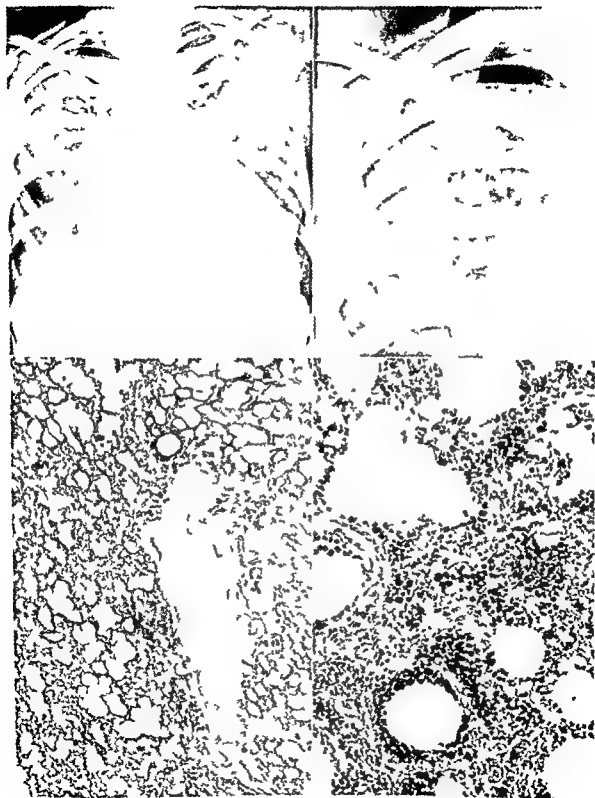


Figure 1 (See legend on next page)

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

previously reported cases Six years later Fleischner and Berenberg were able to collect thirty-one reported cases and cited an additional case of their own Apparently the disease is being discovered more frequently in recent years Idiopathic pulmonary hemosiderosis manifests itself by a sudden onset and recurring seizures of tachycardia, cyanosis, dyspnea, cough, hemoptysis, at times jaundice, in association with hypochromic anemia without evidence of generalized hemolytic tendency The sputum and gastric washings may reveal iron containing macrophages In the late stages of the disease there may be a compensatory polycythemia There is often fever and abdominal pain The seizures last several days and subside With recurring episodes of increasing severity, larger portions of the lungs become involved leading eventually to a fatal outcome The disease is not part of a generalized tosis since there is no general disturbance of iron metabolism The cause of the disease is unknown

At autopsy the lungs are firm, beefy and reddish brown in color Small hemorrhages may be seen on the pleural surface as well as within the lung substance The changes in the lungs are characterized by diffuse interstitial fibrosis, often a necrotizing endarteritis chiefly of the small vessels and an increase in reticulum and muscle which reduce the distensibility of the lungs The resulting blood stasis is followed by hemorrhage with deposition of iron deposits in the tissues Microscopic examination reveals hemosiderin-laden phagocytes in the alveoli, alveolar walls and in the interalveolar tissues The alveolar walls are thickened as is the interstitial parenchyma Lendrum and co workers could find no significant differences in the histologic changes of idiopathic pulmonary hemosiderosis and hemosidero-

sis secondary to mitral stenosis except for the more diffuse nature of the former

The reported cases of idiopathic pulmonary hemosiderosis, summarized by Wyllie and associates, reveal no distinguishing physical features excepting for the occasional presence of clubbing of fingers and evidence of heart failure in the late stages of the disease The disease is characterized roentgenologically by fine, diffuse, mottled infiltrations variously described as having a "smoky," "ground glass," "mossy," or "pumice stone" appearance The involvement is bilateral and is most pronounced in the hilar regions The fine nodules bear superficial resemblance to miliary tuberculosis but on closer inspection the changes are more in keeping with sarcoidosis or lipidosis (Wyllie *et al*) The roentgenologic markings vary with the clinical course of the disease Fleischner and Berenberg note that infection and atelectasis may complicate the roentgen appearance

HEMOSIDEROSIS DUE TO IRON OVERLOAD

Hemosiderosis may follow repeated blood transfusions or excessive parenteral administration of iron The condition has been observed in malnourished Africans with pellagra who subsist mainly on a diet of corn meal It is believed that the iron may come from the utensils used in the preparation of the food The organs chiefly involved are the Kupfer cells of the liver and the other reticuloendothelial cells of the body The nature of the pulmonary involvement has received little study However, one is impressed with reddish brown appearance of the lungs and the pigment laden phagocytes found in the alveolar spaces The experimental studies of Nissen are particularly revealing This investigator found that four hours after intravenous injections of

Figure 12 Hemosiderosis of lungs in association with rheumatic heart disease A (Upper left) Miliary infiltrations in both lungs especially mid thirds heart greatly enlarged B (Upper right) Lung detail showing miliary foci C and D (Lower left and right) Microscopic sections showing focal deposits of dark staining iron pigment in perivascular and interstitial tissues (Autopsy disclosed old rheumatic valvulitis of mitral valve with stenosis and insufficiency, dilatation and hypertrophy of left auricle right ventricle and right auricle, chronic passive congestion and siderosis of lungs chronic passive congestion of liver and spleen) (From Rubin *Diseases of the Chest* W B Saunders Co)

large doses of saccharated iron oxide iron containing leukocytes are seen in the large vessels of the lungs. The lung capillaries also contain large numbers of similar cells while a few larger iron containing cells appear to be held up as capillary emboli.

Womack and Brownlee found reports of twenty five cases of hemosiderosis which occurred after repeated blood transfusions. From the few chest x rays available for study it appears that the roentgen changes consist of a diffuse interstitial reaction resembling that observed in the idiopathic rather than the mitral type of disease. Were chest x rays taken routinely after massive or repeated blood transfusions there is reason to believe that the lungs would be found to be the site of siderotic deposits more often than is realized. A large transfusion of blood or fluid by symptoms and signs of pulmonary edema over a relatively short period may be followed by Roentgenologically one may find a veil like density obscuring both lung fields probably representing acute overload of the lesser circulation. After repeated blood transfusions one may see fine stippling. It is often difficult to interpret the lesions seen in chest x rays of patients with blood dyscrasias because of the difficulty of determining whether they are due to the underlying disease or the result of blood transfusions so often utilized in the treatment. Even the findings at autopsy may not provide an answer. Reported cases of blood dyscrasias associated with pulmonary lesions often neglect to take this factor into consideration.

Case 9 Male—Age 59

Was well until 1945 when he developed a primary polycythemia. The hemoglobin was 17 gms and the red blood cells 6,300,000. The patient was treated with irradiation. Later a diagnosis of myelofibrosis was made and the patient was treated with multiple blood transfusions. He soon developed a greatly enlarged spleen and liver and in time showed increasing jaundice, weakness and urinary tract infections. On admission to the Montefiore Hospital examination revealed a chronically ill appearing man, anemic, icteric with hepatosplenomegaly. Blood and chemical studies also biopsy of an iliac crest confirmed the diagnosis of myelo-

fibrosis and osteosclerosis. Representative blood counts showed hemoglobin ranging from 2.2 to 5.8 gms, red blood cells 0.3 to 1.9 million, white blood cells 17,500 to 39,200 and abnormal differentials.

The patient was initially treated with packed red cells, digitals and mercurials. Because of a comparatively little increase in hemoglobin and progressive increase in the icteric index indicative of progressive hemolysis he was given transfusions of fresh blood with some improvement. He also received cortisone with questionable results although he required less frequent transfusions. During one period of seventy two hours during which he received three transfusions after he had had several in the preceding days a chest x ray showed diffuse small irregular infiltrations throughout both lung fields associated with dyspnea and orthopnea. The picture was in keeping with pulmonary edema. The patient was treated with ACTH and the transfusions were temporarily discontinued. A later chest x ray showed almost complete disappearance of the infiltrations (Figures 13A and B). The patient's course was progressively downhill and he died six months later.

The autopsy showed focal myelofibrosis and osteosclerosis, hemosiderosis of the spleen, lymph nodes, liver and pancreas, periportal fibrosis of the liver, generalized edema of viscera, generalized anasarca and serous effusions and pulmonary edema. The heart was flabby, dilated in all chambers with minimal hypertrophy of the left ventricle. The lungs appeared brownish red with anthracotic pigment. The alveolar spaces were filled with edema fluid.

Although not directly related to the problem it may be appropriate to mention that transfusional hemosiderosis and hemochromatosis with which the former may be confused are distinct entities. Kleckner and co-workers note that transfusional hemosiderosis occurs as often in women as in men, cirrhosis of the liver is lacking or is a coincidental finding and diabetes mellitus and skin pigmentation are infrequent. On the other hand hemochromatosis occurs almost exclusively among men, usually in later life and there is associated cirrhosis of the liver, diabetes mellitus, skin pigmentation and testicular atrophy. The most reliable method of diagnosing hemochromatosis is by needle biopsy of the liver.



Figure 13 Case 9 Pulmonary hemosiderosis secondary to primary polycythemia A (Left) Diffuse small n B (Right) Reticular and nodular and osteo

Polycythemia

Anoxia causes an increase in circulating erythrocytes to augment the oxygen carrying capacity of the blood. The resulting polycythemia is a compensatory mechanism a phenomenon encountered at high altitudes in association with cavernous hemangioma of the lung congenital maldevelopments of the heart and large blood vessels and in a variety of chronic pulmonary diseases including advanced emphysema fibroid tuberculosis and pneumoconiosis. Diseases associated with pulmonary arteriosclerosis are particularly apt to be associated with polycythemia. Polycythemia vera (erythremia) on the other hand is a hematologic disorder characterized by excessive erythropoiesis due to hyperplasia of the red bone marrow. In addition to symptoms of anoxia polycythemia vera is featured by enlargement of the liver and spleen hyperglobulinemia an elevated metabolic rate leukocytosis and other signs pointing to a primary blood dyscrasia. The differential diagnosis between the primary and secondary forms of polycythemia may be quite difficult. Under such conditions the appearance of the chest x ray may be helpful.

Hirsch also Hodes and Griffith note that in patients with polycythemia vera there may be present accentuation of the bronchovascular markings as well as infiltrations and discrete spherical lesions in the midzones of the lungs. The prominence of the truncal shadows is due to vascular engorgement. The discrete nodular lesions are believed to represent thromboses of pulmonary veins although stasis and infarction are also possibilities. On the other hand, in polycythemia associated with pulmonary vascular sclerosis the middle and peripheral zones of the lungs are usually within normal limits in spite of the prominence of the right heart and pulmonary conus. In a study of the chest x ray findings in thirty six patients with polycythemia vera Hodgson and co workers noted varying degrees of parenchymal involvement in twenty five. The abnormalities consisted of bilateral passive congestion increased fibrosis of the bases infiltrations of both lungs and increased bronchovascular markings. The findings of these authors are in agreement with those of Hodes and Griffith. Although cardiac enlargement often

coexists there are a sufficient number without this complication to warrant the conclusion that

DISEASES OF THE BLOOD

the pulmonary changes are probably related to the polycythemia

Hemorrhagic Diseases

Blood dyscrasias associated with an abnormal tendency to bleeding rarely affect the lungs. This is somewhat surprising in view of the vulnerability to hemorrhage of other parts of the body especially the oropharynx and larynx. Blood is pirated from the latter may cause respiratory distress. Freedman and co workers reported one instance of hemophilia and another of thrombocytopenic purpura associated with nontraumatic hemothorax. The patient with thrombocytopenic purpura died and the postmortem examination revealed hemorrhage from the intestinal mucosa perforation of the left diaphragm, a sanguinolent empyema in the left chest and necrosis of the left lower lobe of the lung.

Di Cara reported a case of spontaneous hemothorax in a patient suffering from thrombocytopenic purpura and pulmonary tuberculosis. The treatment of the hemothorax presented great difficulties because of the patient's allergic reactions to blood transfusions. After a stormy course involving treatment with intercostal catheter drainage intrapleural instillation of streptokinase streptodornase and breathing exercises also antituberculous drugs the patient recovered. The author suspected that the cause of the spontaneous hemothorax was probably due to rupture of an adhesion or bulla involving vascular chain.

Nels Di Cara cited a similar case reported by Pitt in 1900 which ended fatally and also the case of Freedman and co workers mentioned above.

In a study of causes of hemorrhagic pleural effusions Berliner did not find a single instance of blood dyscrasia in 120 cases analyzed. Scurvy, purpura and hemophilia as well as cterus and severe anemia are mentioned in Berliner's review as possible causes of hemorrhagic pleural effusions. Pendergrass and Neuhauser described a case of interlobar hemorrhage in a patient with hemophilia. The roentgen shadow simulated a parenchymal lesion. Jersild reported the case of a woman aged twenty two who had Schonlein Henoch purpura. The chest x ray revealed an area of infiltration in the right lung which appeared to be a well organized hematoma. Following administration of vitamin P (citrin) there was complete disappearance of the symptoms. On a previous occasion the same investigator, while treating a number of patients with citrin for hemorrhagic diathesis observed another woman of thirty seven who had hemoptysis and roentgen changes in the lungs. The underlying condition was ascribed to avitaminosis. Under treatment the tendency to hemorrhage and the lung symptoms receded.

Leukemia

Leukemia is a condition in which there is proliferation of the leukoblastic cells of the body in abnormal state usually but not invariably manifesting itself in the blood. When not reflected in the blood the condition is referred to as aleukemic or subleukemic leukemia and the diagnosis is then made by study of the bone marrow. Dimeshek recognizes four classes of leukemia according to the predominant cell type: (1) granulocytic (myelogenous), (2) lymphocytic (lymphatic), (3) monocytic and (4) plasmocytic (multiple myeloma). There are acute chronic and intermediate forms of the dis-

ease. The leukemias are allied to the malignant lymphomas of which Hodgkin's disease and lymphosarcoma are the most prominent members.

There is an erroneous impression that leukemic involvement of intrathoracic structures is unusual although a number of studies have shown the contrary to be the case. Among forty eight cases of leukemia with typical blood pictures Kirklin and Hefl found involvement of the thorax in ten cases. Of these, six were instances of chronic lymphocytic leukemia, two of chronic granulocytic leukemia and two of acute leukemia. A meta-



Figure 14 Acute lymphatic leukemia with intrathoracic manifestations. A (Left) Lobulated density at the left hilum linear horizontal infiltrations in left lower lobe. B (Right) After radiotherapy regression of hilar density linear horizontal infiltrations persist. (Patient eventually died. Autopsy revealed acute lymphatic leukemia involving spleen liver and bone marrow. No evidence of leukemic infiltrations in lungs.)

and Craver found roentgenologic evidence of intrathoracic involvement in 77 per cent of cases of lymphocytic leukemia, the majority revealing enlarged hilar or mediastinal lymph nodes or both. The lung parenchyma was involved in 24.6 per cent and the pleura in 17 per cent; a pleural effusion being demonstrable in 17 per cent. The incidence of intrathoracic involvement in granulocytic leukemia was found to be much less. Of fifty-two cases of the latter, discrete nodes at the lung roots were present in chest x-rays in 9.6 per cent and parenchymal infiltrations in 7.6 per cent. Bichel in a study of 217 cases of leukemia could find no definite evidence of mediastinal changes in any of the granulocytic leukemias but in the chronic lymphocytic type it was usual to find on roentgen examination some degree of hilar lymph node involvement. The high incidence of intrathoracic involvement, especially in the lymphocytic type of leukemia, is mentioned by Falconer and Leonard and others.

As is true of intrathoracic lymphomas as a group and thus applies especially to the leukemias, the physical examination of the chest gives little information. Excepting cases in which large mediastinal tumors are present, usually thymic in origin, bronchial obstructive phenomena such as wheezing, respiration and sputum retention are

uncommon. If the mediastinal tumor is unusually large, there may be cough, seizures of dyspnea, especially in the prone position, and signs of pressure on the superior vena cava. Inasmuch as the disease is not of a directly invasive nature, there is rarely evidence of involvement of the sympathetic recurrent laryngeal or phrenic nerves. The presence of a Horner's syndrome or a paralyzed diaphragm in a patient with a mediastinal mass speaks more for carcinoma.

The roentgen manifestations of the leukemias do not differ significantly from those encountered in Hodgkin's disease or lymphosarcoma, excepting for the possibly larger tumefactions encountered in the latter. The most frequent findings are enlarged hilar lymph nodes with little if any evidence of extension of the process into the adjoining lung tissue (Figures 14A and B). If the latter is grossly involved, the permeation is along peribronchial and perivascular channels. Isolated pulmonary infiltrations are seldom recognized roentgenologically, although often seen on histological examination of tissues (Figures 15A and B). Joachim and Loew reported a unique case of granulocytic leukemia featuring roentgenologically by patchy migratory infiltrations in both lungs. These were believed to be either embolic or infective in nature. The findings at

autopsy were in keeping with repeated infarctions secondary to vascular occlusions.

Nathan and Sanders studied fifty-nine autopsied cases of acute leukemia. They noted that hilar lymph node involvement and pleural effusion were frequent but gross lung involvement is rare. However, on microscopic examination they found fourteen or 23.7 per cent to have

definite leukemic involvement of the pulmonary parenchyma, chiefly in the walls of the alveolar septum near small bronchioles and blood vessels and subpleurally. Except for the occasional presence of a pleural effusion, the chest x rays are usually negative so far as pulmonary lesions are concerned.

Myeloma

This disease occupies a position somewhere between frank tumors and leukemias. The growths, usually arising in bone marrow are composed of myeloid cells which resemble plasma cells. On rare occasion the myeloma may be solitary and amenable to surgical extirpation as illustrated by a case previously reported by the writer. The patient, a white male fifty-eight years of age, was found to have at operation a solitary myeloma of a rib. It was excised successfully. Three years later the patient died of coronary thrombosis without clinical evidence of recurrence of the disease. I have since encountered a similar instance (Figures 16 A and B).

Galagno believes that, so called, 'solitary myeloma' if followed long enough, will eventually become multiple. As illustrated in Figure 16, when a myeloma involves the thoracic cage, the growth seldom invades the pleura or lung but simply displaces the latter. Much more often there is diffuse myelomatosis of bone marrow. In addition to skeletal involvement, which often results in pathologic fractures, the diagnosis rests on the finding of Bence-Jones proteinuria, anemia, nephritis and azotemia, in one combination or another.

Of particular interest, from the viewpoint of the present discussion, is the frequency of pneu-



Figure 15 Chronic myelogenous leukemia with intrathoracic lesions. A (left) Minute infiltrations scattered throughout right lung especially upper lobe; infiltrations and linear striations in left lower lobe, enlarged hilar lymph nodes. B (right) Lung detail (Patient died). Histologic examination of lung tissue revealed immature myeloid cells and polymorphonuclear cells in perivascular and peribronchovascular thickened interlobular septa permeated with similar cells; myeloid cells in capillaries and in walls of bronchioles; hilar and tracheobronchovascular lymph nodes enlarged and invaded by many myeloid cells.



Figure 16 Myeloma with intrathoracic lesions. A (Left) Well demarcated density in right upper lobe at level of third rib anteriorly. Circumscribed rounded density in right paravertebral gutter at level of T3 and 4. Fractures of right and left lower ribs. Localized bulging of diaphragm. B (Right) Oblique view showing position of the two masses. (At operation well circumscribed soft hemorrhagic fleshy tumors were found situated peripherally at the sites indicated related to rib structures. The chest wall lesion was internal to ribs and external to pleura and lung. The lesion in the paravertebral gutter was also external to lung and pleura. Contiguous ribs were eroded and showed pathological fractures. Both tumor masses were excised. The histologic picture was in keeping with a plasma cell myeloma.)

monia in patients with multiple myeloma. Zinne-
man and Hall reviewed the clinical records of
sixty-four patients with multiple myeloma. Thirty-
seven had bouts of bacterial pneumonia and in ten
of these it was recurrent. A man of sixty-three
was recently admitted to the Montefiore Hospital
with complaints of cough, fever and chest pain.

During a period of four years this patient had
been treated for multiple myeloma and on six
occasions had been hospitalized with clinical and
chest x-ray findings in keeping with transient
episodes of pneumonia. Pneumonia and bronchi-
ectasis are also a feature of agammaglobulinemia
because of poor antibody response to infection.

Infectious Mononucleosis

Glandular fever or infectious mononucleosis is,
in the vast majority of cases, a self-limited disease
occurring sporadically or in small epidemics. The
intensity of the seizure varies considerably in dif-
ferent individuals and is apt to be more acute
during epidemics. The disease is most likely
caused by a virus although a specific agent has
not been isolated. Infectious mononucleosis
affects mainly young people; in fact, the most
detailed studies of the disease have been made in

Army station and Veteran Administration Hos-
pitals. To explain the unusual age incidence, the
increased seasonal incidence, the fruitless results
of attempts at experimental transmission and the
absence of transmission to room- and ward-mates,
Hoagland postulates that the disease is trans-
mitted chiefly by oral contact which allows for sal-
ivary exchange and that the incubation period of
the disease is about thirty-three to forty-nine
days.

Infectious mononucleosis, in its classical form, is characterized by fever, malaise, sore throat, enlargement of lymph nodes, splenomegaly, skin eruptions and abdominal complaints. The disease is protein in its manifestations and may involve diverse organs, including the central nervous, cardiovascular, digestive and respiratory systems as well as hemopoietic organs.

As the name implies, infectious mononucleosis is featured by hematologic findings. The characteristic cell of infectious mononucleosis is an immature, "leukocytoid" lymphocyte which is present in lymph nodes, tissues, bone marrow and blood. The lymphocytes vary in size, in the appearance of the cytoplasm, in the size and shape of the nuclei and in their ability to take up stain. The mononuclear count is usually much higher in sporadic cases than during epidemics. In a study of 556 cases observed in a military hospital, Wechsler and co-workers found an initial, transient leukocytosis, varying between 10,000 to 20,000 cells, or a normal count, followed by a drop to either normal or leukopenic values. An increase in mononuclear cells was usually evident after the third day of the disease, the percentage ranging in most instances between forty and fifty. Schultz and Hall, in a study of 100 cases, found that during convalescence there is occasionally an eosinophilia.

In addition to the physical and hematological findings, the heterophile antibody agglutination test of Paul-Bunnell, using sheep cells, is a valuable diagnostic aid. It should be noted that the test has been found positive in high titer in a considerable number of other diseases. The Davidsohn absorption tests, using guinea pig kidney and boiled beef erythrocytes, is of additional value. A frequent observation is in abnormally high incidence of disturbed liver function found in as high as 90 per cent of the cases. Sera of patients with infectious mononucleosis may give false positive reactions for syphilis, typhoid and undulant fever. As might be expected, the differential diagnosis often includes enteric diseases as well as acute leukemia, poliomyelitis and infectious hepatitis.

Respiratory tract involvement, although seldom striking, occurs quite often. The most fre-

quent symptoms, aside from those referable to the throat and upper air passages, are croupy cough, wheezing respiration and substernal discomfort. These are often related to enlarged hilar lymph nodes. In addition, there are symptoms indicative of tracheitis and bronchitis. In a few, signs of pneumonia may be present with high fever, chill and evidence of pulmonary consolidation. As a rule, the physical findings of pulmonary involvement are minimal and do not parallel the extent of the roentgen changes. In fact, the chest x-ray may reveal abnormal findings in the absence of clinical signs.

The chest x-rays may reveal enlarged hilar lymph nodes, often in association with perivascular patchy infiltrations in both lungs. Occasionally, there may be massive densities. McCort studied the chest x-ray findings of forty-three patients with infectious mononucleosis. In six patients there were changes which could be attributed to the disease. An additional case studied on another occasion was included in the group. Enlargement of the mediastinal lymph nodes were noted in two cases. Both enlargement of the mediastinal lymph nodes and pulmonary parenchymal changes were noted in three cases. Parenchymal changes only were noted in two cases. Wechsler and co-workers found, in four teen of 556 cases of infectious mononucleosis, roentgen changes in the lungs similar to those encountered in primary atypical pneumonia.

The exact nature of the pneumonia occurring in the course of infectious mononucleosis is not always ascertainable since individuals rarely die of uncomplicated disease. In some, the disease represents a secondary infection, in others, the two conditions occur simultaneously, apparently caused by the same agent. Allen and Kellner had a unique opportunity of being able to examine the organs of a pilot who had had a recent seizure of infectious mononucleosis and who died immediately after an aviation accident. A chest x-ray taken at the time of the initial hospitalization revealed a definite increase in the vascular and peribronchial markings of the right lung. The hilar markings were also prominent. The tentative diagnosis was primary atypical pneumonia, etiology unknown. A blood count of 11,450

white cells with 14 per cent neutrophils, 77 per cent lymphocytes and 9 per cent monocytes, as well as the obtainment of the heterophil antibody titer of 1 896, made it evident at the time of hospitalization that one was also dealing with infectious mononucleosis. Examination of the lungs after death revealed many nodular collections of mononuclear cells and lymphocytes in relation to bronchi and blood vessels but often within the interstitial tissues. In the light of these findings, the authors considered it most likely that the roentgen appearances, ascribed initially to a primary atypical pneumonia, represented mononucleosis infiltrations of the lungs.

A detailed review of the pathology of infectious mononucleosis was published by Curtis and Smith. The study was based on nine autopsies, including the one of Allen and Kellner cited

above, also the examination of more than 100 lymph node biopsies and additional material obtained from the files of the Army Institute of Pathology. With respect to the respiratory tract it was noted that in two cases there was frank pneumonic consolidation, the cellular exudate in one being of the polymorphonuclear neutrophil type and in the other of the large lymphoid type. Most cases showed exaggeration of the peribronchial and bronchovascular tissues and, in some, the round cell reaction extended along the intra-alveolar septa to simulate interstitial pneumonitis. The actual involvement of lung tissue was slight in five, prominent in three and absent in one. These authors also draw attention to the frequency of symptoms and signs of atypical pneumonia in patients with infectious mononucleosis, especially at the onset of the disease.

Bibliography

PULMONARY DISEASES ASSOCIATED WITH UNUSUAL BLOOD FINDINGS

- BURGER E A. Leuko Erythroblastic Anemia Due to Bronchogenic Carcinoma. *Dis Chest* 18:57 1950
- CONF R B and NAYER H B. Thrombocytopenic Purpura in Association with Primary Bronchogenic Carcinoma. *Am Rev Tuberc* 67:509 1953
- FAHEY M J. Unusual Leukocyte Responses in Primary Carcinoma of the Lung. *Cancer* 4:930 1951
- FITZPATRICK W J and SCHWARTZ S O. Polycythemia Secondary to Tuberculosis of the Spleen. *Am Rev Tuberc* 60:660 1949
- FOUNTAIN J R. Blood Changes Associated with Disseminated Tuberculosis. *Brit M J* 7:76 1954
- HECK F J and HALL B E. Leukemoid Reactions of the Myeloid Type. *J A M A*, 112:96 1939
- HENDRY A T. Purpura and Tuberculosis. *Tubercle* 36:294 1955
- HENKIN W A. Bronchogenic Carcinoma. A Clinical Pathological Study of 36 Autopsied Cases seen at the Brooklyn Cancer Institute between 1937 and 1945 inclusive. *Ann Int Med* 27:743 1947
- HILL J M and DUNCAN C N. Leukemoid Reactions. *Am J M Sc* 70:847 1941
- HUMPHRIES G H Jr and SOUTHWORTH H. Aplastic Anemia Terminated by Removal of a Mediastinal Tumor. *Am J M Sc* 70:501 1945
- ISAACSON N H and RAPOPORT P. Eosinophilia in Malignant Tumors. *Ann Int Med* 75:893 1946
- JAFFE R H. Tuberculosis and Leukemia. *Am Rev Tuberc* 78:32 1933
- KRUMHOLTZ E B. Leukemoid Blood Pictures in Various Clinical Conditions. *Am J M Sc*, 172:519 1956
- KUTNER J F, LINTARIS L R, SPIGA W W, FOWLER W M and LUBRIZ J M. Clinicopathological Conference. *Ann Int Med*, 42:945 1955

- LANDOUZY L. A Note on La Typho Bacilliose. *Lancet* 2:1440 1908
- LEIBOWITZ S. Tuberculous Sepsis with a Myeloblastic Blood Picture. *Arch Path* 21:363 1938
- LISA J, SOLOVICH C and GORDON E J. Leukemoid Reaction in Carcinomatous Skeletal and Splenic Metastases. *Am J Cancer* 40:227 1940
- MARZELLO E R, and DEVEER J A. Tuberculosis Simulating Acute Leukemia. *Am J M Sc*, 187:372 1951
- RENNER H. Über Sepsis tuberculosis gravissima bei einem Falle von Polycythämie. *Beitr Klin Tuberk* 53:197 1952
- REUBIN C H. Haematogenous Tuberculosis in the Adult. I. Generalized Haematogenous Tuberculosis. *Am Rev Tuberc* 39:557 1939
- REUBIN C H. Haematogenous Tuberculosis in the Adult. II. Haematogenous Pulmonary Tuberculosis. *Am Rev Tuberc* 40:667 1939
- SINGER K and DANESHEK W. Symptomatic Hemolytic Anemia. *Ann Int Med* 15:544 1941
- STATZ D, ROSENTHAL N, and WASSERMAN L R. Hemolytic Anemia Associated with Malignant Diseases. *Am J Clin Path*, 17:585 1947

SICKLE CELL ANEMIA

- CARROL D S, and EVANS J W. Roentgen Findings in Sickle Cell Anemia. *Radiology* 53:814 1949
- DIGGS L W, and CHENG H E. Pathology of Sickle Cell Anemia. *South M J* 77:939 1934
- HENDERSON A B. Sickle Cell Anemia. *Am J Med* 9:757 1950
- HERRICK J B. Peculiar Elongated and Sickle Shaped Red Blood Corpuscles in a Case of Severe Anemia. *Arch Int Med* 6:517 1910
- WARGOLDES M P. The Incidence of Sickness. *Am J M Sc* 221:270 1951

- ROSENBERG, R., KARBON, B., LICHTMAN, H. C. and LYONS, H. A. Sickle Cell Trait and Disease in Pulmonary Tuberculosis *Arch Int Med*, 95 540 1955
- SCOTT, R. B., BANKS, L. O., JENNINGS, W. F. and CRAWFORD, R. P. Studies in Sickle Cell Anemia II Clinical Manifestations of Sickle Cell Anemia in Children *J Pediatr* 39 400 1951
- WEISS, W. and STECHER, W. Tuberculosis and the Sickle Cell Trait *Arch Int Med* 89 914 1957
- WEISS, W. and WAITE, S. O. Sickle Cell Anemia and Tuberculosis *Am Rev Tuberc* 65 735 1952

PULMONARY HEMOSIDEROSIS

- AMPAUGH, W. E. Pulmonary Hemosiderosis *Am J Roentgenol* 41 597 1959
- CARLEN, W. Handboken der sje seltan patologiellen Anaemie i Histologie by F. Henke and O. Lubarsch *Jna* 20 1931
- ELEVENAAR, O. and KJELLBERG, S. R. Hemosiderosis of the Lungs—Typical Roentgenological Findings *Acta radiol* 29 32 1948
- ENTICKAMP, J. B., MILSTEIN, B. B. and BAKER, C. Lingular Biopsy in Mitral Stenosis *Thorax* 9 18 1954
- ESPOSITO, M. J. Focal Pulmonary Hemosiderosis in Rheumatic Heart Disease *Am J Roentgenol* 73 351 1955
- FLEISCHNER, F. G. and BERENBERG, A. L. Idiopathic Pulmonary Hemosiderosis *Radiology* 62 572 1954
- GLUMPER, T. E. Military Appearances in the Lungs in Mitral Stenosis Endogenous Pulmonary Hemosiderosis *Brit M J* 2 488 1947
- KENT, G., GILBERT, E. S. and MEYER, H. H. Pulmonary Microthrombi *Arch Pathol* 60 556 1955
- ALLEN, M. S. J. B. B. G. S. A. H. and WEIN, J. F. Hemochromatosis and Transfusional Hemosiderosis *Am J Med* 16 387 1954
- LAUSOV, H. M. Diverted Ossification of the Lungs in Association with Mitral Stenosis *Brit M J* 1 431 1949
- LENDUM, A. C., SCOTT, L. D. W., and PARK, S. D. S. Pulmonary Changes Due to Cardiac Disease with Special References to Hemosiderosis *Quart J Med* 19 749 1950

- McLEITCH, V. G. B. and COLPITTS, G. Essential Brown Induration of the Lungs *Canad M J A J* 61 129 1949
- ULMIRAD, E. E., GRAY, G., JONES, F. and HILL, J. M. Iron Overload (Hemosiderosis) Aggravated by Blood Transfusions *Arch Int Med* 83 47 1949
- NANCYVILLE, L. Acute Idiopathic Pulmonary Hemosiderosis *Brit M J* 1 431 1949
- PARAZA, F., JR. and WEISS, S. The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis *Am J Pathol* 17 173 1956
- PENDEBARKIS, I. P., LAMIE, L. L. and OSTREICH, H. W. Hemosiderosis of the Lung Due to Mitral Disease *Am J Roentgenol* 61 443 1949
- PULCHER, J. D., and FITZGERALD, O. Pulmonary Hemosiderosis in a Six Year Old Boy *Am J Dis Child*, 67 38 1944
- RENN, E. H. Diseases of the Chest Philadelphia W. B. Saunders Company 1947 p 61
- SCHEIDT, S. O., and BILLYNIE, S. A. Foreign Body Pulmonary Hemosiderosis Resulting from Blood Transfusions *Blood* 3 617 1948

- SCOTT, L. D., PARK, S. D. S. and LENDUM, A. C. The Clinical Radiological and Pathological Aspects of Pulmonary Hemosiderosis *Brit J Radiol*, 30 100 1947
- TUTT, G. B. and CORRIJN, M. Idiopathic Pulmonary Hemosiderosis *Thorax* 7 307 1951
- TAYLOR, H. I. and STRONG, G. F. Pulmonary Hemosiderosis in Mitral Stenosis *Am J Med*, 47 76 1955
- WALDESTEIN, J. Relapsing Diffuse Pulmonary Bleedings or Hemosiderosis Pulmonum *Acta Radiol* 25 149 1944
- WISSEMAN, W., WOLFE, D. and VERLOOF, M. C. Idiopathic Pulmonary Hemosiderosis *Acta med scandinav*, 146 341 1953
- WONACK, C. R. and BROWNLEE, R. G. Jr. Hemosiderosis Following Repeated Blood Transfusions *Am Pract & Digest Treat* 1731 1950
- WILLIE, W. G., SHELDOVE, W., BOONAN, M. and BARON, A. Idiopathic Pulmonary Hemosiderosis (Essential Brown Induration of the Lungs) *Quart J Med* 17 55 1949
- YATES, J. L. and THALUNGER, W. Treatment of Pernicious Anemia: A Patient Who Received One Hundred and Thirteen Transfusions *J A M A*, 87 1154, 1916

POLYCYTHEMIA

- HIRSCH, I. S. Pulmonary Changes in Polycythemia Vera *Radiology* 26 469 1956
- HONES, P. J. and GRIFFITH, J. Q. Chest Roentgenograms in Polycythemia Vera and Polycythemia Secondary to Pulmonary Arteriosclerosis *Am J Roentgenol* 46 57 1941
- HOOVER, J. H., GOOD, C. A., and HALL, B. E. The Roentgenographic Aspects of Polycythemia Vera *Proc Staff Meet Mayo Clin* 21 157 1946
- WASSERMAN, L. R. Polycythemia Vera: Its Course and Treatment Relation to Myeloid Metaplasia and Leukemia *Bull New York Acad Med* 30 343 1954

HEMORRHAGIC DISEASES

- BERLINER, A. Hemorrhagic Pleural Effusion: An Analysis of 170 Cases *Ann Int Med*, 14 166 1941
- DiCARA, L. V. A Rare Case of Spontaneous Hemorrhax *Am Rev Tuberc* 71 755 1955
- FOX, J. R., SPENCER, J. T., JR., and TOLAN, L. M. Dyspnea in Hemophilia from Hemorrhage into Larynx *JAMA* 130 78 1946
- FREEDMAN, P., LEVINE, S., and SOLIS COHEN, L. Hemorrhage in Blood Dyscrasias *Am J Med Sci*, 205 499 1943
- JERVIS, T. Haemoptysis and Lung Infiltration Caused by Arteriovenous *Lancet* 236 617 1936
- JERVIS, T. Therapeutic Effect of Vitamin P in Schonlein-Henoch Purpura *Lancet* 234 1445 1938
- PENDEBARKIS, F. P., and NEUBAUER, F. B. D. Pleural Lesions in Hemophilia *Am J Roentgenol*, 48 147 1947

LEUKEMIA

- BENNETT, J. Metastatic Tumors in Leukosis *Acta Radiol*, 51 81 1950
- DANIELS, W. The Outlook for the Leukemic Control of Leukemia *Acta England J Med*, 190 131 1954
- FELDMAN, I. H. and LEVISON, M. F. Pulmonary Involvement in Lymphosarcoma and Lymphatic Leukemia *J Am Sc.*, 195 294 1958

- JOACHIM, H. and LOEW, L. Atypical Acute Myeloid Leukemia With Unusual Pulmonary Manifestations *Am J M Sc*, 171:215 1927
- KIRKIN, B. R. and HEFKE, H. W. Roentgenologic Study of Intrathoracic Lymphoblastoma *Am J Roentgenol* 26:681 1931
- LEVISON, A. B. Respiratory Obstruction in Acute Leukemia *Lancet*, 1:1151 1935
- NATHAN, D. J. and SANDERS, M. Manifestations of Acute Leukemia in the Parenchyma of the Lung *New England J Med* 252:797 1955
- VIETA, J. O. and CRAVER, L. F. Intrathoracic Manifestations of the Lymphomatoid Diseases *Radiology* 37:138 1941
- CLUSTER, R. P. and SMITH, F. B. The Pathology of Infectious Mononucleosis *Blood*, 3:830, 1948
- DAWSON, I. Heterophile Antibodies in Serum Disease *Third Report J Infect Dis*, 41:219 1933
- HAGLAND, R. J. The Transmission of Infectious Mononucleosis *Am J M Sc*, 229:262 1955
- McCOY, J. J. Infectious Mononucleosis With Special Reference to Roentgenologic Manifestations *Am J Roentgenol* 62:643, 1949
- PALL, J. R. and BLUNELL, W. W. The Presence of Heterophile Antibodies in Infectious Mononucleosis *Am J M Sc* 183:90 1932
- READ, J. T. and HELWIG, F. C. Infectious Mononucleosis *Arch Int Med* 75:376, 1945
- RODSTEIN, M. A Case of Infectious Mononucleosis with Atypical Pneumonia *Ann Int Med*, 28:1177 1948
- SCHULTZ, A. L. and HALL, W. H. Clinical Observations in 100 Cases of Infectious Mononucleosis and the Results of Treatment With Penicillin and Aureomycin *Ann Int Med*, 36:1498 1952
- WECHSNER, H. F. ROSENBLUM, A. H. and SILLS, C. T. Infectious Mononucleosis Report of an Epidemic in an Army Post *Ann Int Med* 25:113 1946
- YOUNG, L. E., STOREY, M. and REDMOND, A. J. Clinical and Epidemiological Features of an Outbreak of Primary Atypical Pneumonia of Unknown Etiology Among Hospitals and Medical School Personnel *Am J M Sc*, 206:756, 1943
- ZIEGLER, E. C. Infectious Mononucleosis Report of a Fatal Case with Autopsy *Arch Path*, 37:196 1944

MYELOMA

- BALTON, O. C. Agammaglobulinemia *Pediatrics* 9:722 1952
- GALAGANO, A. R. Unusual Features of Multiple Myeloma *Am J Roentgenol* 74:304 1955
- GOOD, R. A. and MAZZITELLO, W. F. Chest Disease in Patients with Agammaglobulinemia *Dis Chest*, 29:9 1956
- RLBIN, E. H. *Diseases of the Chest* Philadelphia W. B. Saunders Company 1947 p 622
- ZINNEMAN, H. H. and HALL, W. H. Recurrent Pneumonia in Multiple Myeloma and Some Observations on Immunologic Response *Ann Int Med*, 41:1157 1954

INFECTIOUS MONONUCLEOSIS

- ALLEN, F. H. and KELLNER, A. Infectious Mononucleosis An Autopsy Report *Am J Path*, 23:463 1947

Allergic Diseases

THE NUMBER of diseases ascribable wholly or in part to allergic causes is considerable and the list is growing. It has been estimated that approximately 10 per cent of the population suffers from some form of hypersensitivity chiefly bronchial asthma and hay fever. Of those normally non-allergic many become sensitized after injections of antitoxin or serum or after medication with various drugs. Since the introduction of sulfonamides penicillin streptomycin and other antibiotics increasing numbers are also developing

Introduction

sensitivity to these agents. Brown published an abbreviated list of 217 drugs and antibiotics which have been found to be associated with allergic reactions. This investigator believes that approximately 500 different drugs can be proved to be sensitizing substances. Even the use of ACTH and cortisone to combat hyperergic states may in turn cause allergic reactions. It is obvious therefore, that allergic diseases constitute a sizable segment of human illness.

Tissue Changes in Allergy

Allergy is not simply an expression of the union of allergin and reagin but as Selye and others have pointed out a complex biochemical phenomenon triggered by a host of stimuli which call forth a pituitary adrenal reaction in response to stress. The characteristic allergic reaction is featured by a sudden often explosive onset rapidly reaching a climax and a slow resolution. Although as a rule the tissue changes parallel the intensity of the reaction there may be considerable variation. At one extreme one meets with violent functional derangements even sudden death without demonstrable changes in the tissues as may occur in anaphylactic shock, at the other with quite reversible inflammatory changes which the individual is able to weather and is left none the worse as a result. Between these two extremes one encounters various degrees of hypersensitivity reactions. It is often difficult to correlate the tissue changes with an allergic cause and this becomes increasingly so with the passage of time. In the scale of allergic reactions there may be degenerative necrotizing proliferative and granulomatous changes or a combination of these. As the various elements entering into the allergic reaction become more complex especially if the irritation is chronic or of low intensity and depending on the nature of the shock organs, the tissue changes are apt to lose any distinguishing features. A surge is eventually reached where it becomes impossible to correlate the nature of the tissue changes with his hypersensitivity except for indirect evidence in the way of an allergic family or personal history, possibly significant hematologic findings but inconclusive treatment and similar suggestive but inconclusive indices. Finally, one meets with a number of diseases the allergic nature of which is highly speculative. Several of the so called collagen or ill defined diseases to be described later fall in this group. There is increasing evidence that hypersensitivity probably underlies the majority of these conditions. If hypersensitive lungs like other organs may react to an excitant with varying degrees of in

tensity, ranging from an evanescent seizure of bronchospasm to chronic bronchiolar obstruction, transitory or protracted eosinophilic infiltrations often associated with polyserositis and eosinophilia, pneumonia, diffuse vasculitis, interstitial fibrosis or a combination of these and other 'morphological equivalents'. Sooner or later secondary infection of the lung supervenes and obscures the basic pathological changes. Anulogous tissue reactions may take place in other parts of the body concurrently or consecutively

which may or may not be clinically apparent. At times, the symptom complexes express themselves in bizarre syndromes. In adulthood the respiratory tract is particularly vulnerable to allergic irritation as exemplified in bronchial asthma and hay fever. With advancing years, the heart and kidneys bear the brunt. The reticulo-endothelial system, composed of a reactive group of cells found chiefly in the lymph nodes, spleen, liver, bone marrow and loose connective tissue take an active part.

Bronchial Asthma

Bronchial asthma represents a state of hypersensitivity of the respiratory tract to air borne or blood borne excitants. The disease is brought about by various factors: extrinsic, intrinsic or a combination of both. Studies of the incidence of the various allergies including bronchial asthma, reveal a family history in over 50 per cent. The factor of heredity is strikingly shown in studies of large families whose health records can be traced back for several generations. Particularly revealing is the incidence and types of allergies occurring in single ovum twins. In these the age of onset of the disease, its severity and the nature of the offending allergens show remarkable parallels: the stronger the family taint, the more sensitive the individual to all manner of excitants.

As typified in the allergic skin reaction the features of which have been studied intensively by Kline, hypersensitivity of lung tissue to an irritant is also characterized by an outpouring of edema fluid. In the bronchi the exudate soon becomes viscid due admixture of mucus from secreting glands. An acute, nonbacterial inflammatory reaction is established around blood vessels. In uncomplicated asthma the vascular response is relatively mild, of limited extent and reversible. In protracted asthma, the vascular response is more profound with eventual desquamation of epithelium distention of mucous glands hypertrophy of the elastic fibers and of the circular muscles of the bronchi and dilatation of the bronchioles and alveoli. Secondary infection soon complicates the process. In hyperergic states the perivascular and vascular reactions are

intense and are apt to be followed by permanent tissue damage.

It may be mentioned at this point that although an excess of eosinophils in the blood (more than 300 per cu mm) as well as in the tissues, sputum, serous effusions and other excreta characterizes the allergic reaction, the absence of eosinophilia does not rule out allergy. In fact, profound hypersensitivity states associated with marked depression of the adrenal cortex may be accompanied by temporary suppression of the eosinophil response. On the other hand, various parasitic infestations, infectious diseases of the hematopoietic organs and even, on rare occasion malignant neoplasms may be associated with eosinophilia (see Table 9).

CLINICAL FEATURES

The symptomatology of bronchial asthma ranges the gamut of transitory seizures of wheezing to a status asthmaticus. The pulmonary manifestations are related chiefly to bronchial obstructive phenomena caused by sputum retention. The secondary infection of the distal portions of the lung soon gives rise to a symptomatology of its own. The type of asthma, whether it be of the, so called extrinsic or intrinsic variety, has an important bearing on the course of the disease. Extrinsic asthma is caused by inhalation of pollen of weeds, grasses and trees, dusts, animal emanations and molds. The disease appears at a relatively early age in persons with decided allergic family histories. Additional signs of hypersensitivity are often present in the form of atopic

dermatitis allergic rhinitis drug and food idiosyncrasies Other significant features include the obscurement of positive skin reactions in offending allergens minimal evidence of bronchopulmonary infection and usually a satisfactory response to antasthmatic medication The prognosis is relatively good

Intrinsic or bacterial asthma is characterized by its appearance later in life in individuals without an allergic background A nondescript respiratory infection often antedates the onset of symptoms After the establishment of the pulmonary infection the individual becomes susceptible to recurring cough expectoration wheezing and increasing dyspnea The symptoms may be temporarily improved by expectorants and antibacterial treatment seldom by the extrinsic variety because the prognosis with it is decidedly worse the repeated damage sustained by the lungs is a result of recurrent infections and the fact that the accompanying fibrosis and emphysema may lead in time to chronic cor pulmonale

ROENTGENOLOGY

The roentgen findings of bronchial asthma the subject in which we are particularly interested at the moment reflect the sequelae of bronchial obstruction and infection also the intensity and duration of these factors The damage sustained by the pulmonary blood vessels is usually minimal and is seldom evidenced roentgenologically However in certain hyperergic states to be discussed later the vascular component may be reflected in certain roentgen changes Chronic bronchial asthma is associated with recurring bronchospasm causing an accumulation of thick tenacious secretion in the air passages The resulting trapping of air in the alveoli due to the reflex narrowing of the air passages during the expiratory phase of respiration lead to a gradual accumulation of air in the alveoli This results in obstructive or so called hyperpneumic emphysema the most frequent by product of chronic bronchial asthma

During an acute asthmatic seizure the chest x-ray may reveal evidence of acute overdisten-

tion of the lungs as seen in the hyperillumination of the lung fields the enlargement of the thoracic cage and depression of the diaphragm the excursion of which is diminished After the subsidence of the initial acute seizures the roentgen markings resume their previous normal state With recurring episodes the hyperillumination of the lungs becomes permanent the ribs occupying a more-or less fixed horizontal position the intercostal spaces becoming wider The vascular and hilar markings become more prominent and there is increasing kyphosis of the chest In the lateral projection the width of the retrosternal space is increased and also shows hyperillumination At this stage one may also discern bullous formations within the lungs and blebs at the periphery In addition to the generalized overdistention of the lung resulting from diffuse obstruction of the lung resulting of sputum obstructing bronchi may cause transitory segmental atelectasis (Figure 17) If a large bronchus is involved lobar or massive atelectasis of an entire lung may result

Increasing alveolar distention and disruption may produce large air pockets within the lungs (bullous emphysema) and blebs in the pleura both of which may give rise to complications Advanced degrees of bullous emphysema may give a picture of a vanishing lung Air escaping from ruptured elastic alveoli may pass along blood vessels and bronchi to the mediastinum causing pneumomediastinum Ruptured blebs on the pleural surface may give rise to pneumothorax on one or repeated occasions Once intrasternal emphysema is established air may escape along fascial planes to the neck chest and abdominal cavity giving rise to variable degrees of subcutaneous emphysema In one instance which I had occasion to treat the escaped air could be traced along muscle planes as far down as the lower extremities If the pressure is sufficiently high air may escape into the abdomen and give rise to retroperitoneum and a detailed discussion of these and other complications of bronchial asthma including the effects of physiological alterations within the thoracic cage is a result of the emphysematous state is beyond the scope of these pages To illustrate the sequence of



Figure 18 Case 10 Tension pneumothorax in an asthmatic after an injection of histamine A (Left) Pneumothorax collapsing the right lung; an air-filled bleb is faintly seen at the upper pole of collapsed lung; right leaf of diaphragm depressed, flattened and showing costal demarcations B (Right) Five weeks later lung has expanded

sideration are characterized histologically by an interstitial nonbacterial mononuclear inflammation the latter consisting chiefly of eosinophilic leukocytes serous membrane exudation and variable degrees of necrotizing vasculitis especially of the small arteries The involvement of the latter determines the intensity and permanence of the tissue damage Roentgenologically these conditions are featured by diffuse infiltrations of patchy or massive proportions and transient pleural effusions A characteristic feature is the presence of eosinophilia also a high eosinophil content of the serous effusions sputum nasal discharges and other body fluids

TRANSITORY PULMONARY INFILTRATIONS AND EOSINOPHILIA (Loeffler's Syndrome)

The association of fleeting infiltrations in the lungs and eosinophilia was brought to general medical attention by Loeffler in 1932 The condition has since been referred to as Loeffler's syndrome although there are now a number of variants of the original description Under an all inclusive title infiltrative eosinophilia

Dias Rivera and co workers list no less than eighteen eponyms for the condition The authors include in this group various parasitic infestations as well as diseases without any recognizable cause For the present we are concerned with such forms of the disease which may be ascribed to constitutional hypersensitivity although a clear cut distinction between the several conditions which may give rise to the disease is not possible on the basis of hypersensitivity alone

The nature of the pulmonary infiltrations in Loeffler's syndrome are detected only in chest x-rays often accidentally The infiltrations remain in the lungs for a few weeks and disappear without leaving any trace At times the pulmonary involvement is widespread In the vast majority the infiltrations represent patches of eosinophilic pneumonia in allergic individual a history of bronchial asthma being often obtained As mentioned an excess of circulating mature eosinophils in the blood is a feature of the disease The blood eosinophilia may reach as high as 70 per cent of the total leukocyte count more often the eosinophil percentage is in the neighborhood of twenty The leukocyte count is

moderately increased The following case is a typical example

Case 11. Male—Age 7 years

A Negro boy with a history of repeated seizures of bronchial asthma was admitted to Seton Hospital for treatment of suspected pulmonary tuberculosis In the three months previously the patient had been treated in another institution for a respiratory infection characterized by shortness of breath wheezing fever and nonproductive cough The chest x ray findings were interpreted as representing patches of bronchopneumonia involving especially the right midlung For a time the chest x rays showed clearing but the infiltrations soon

The day after admission to Seton Hospital the boy became acutely ill with a typical asthmatic seizure associated with wheezing and fever The symptoms responded to antiasthmatic treatment over a period of two weeks Of particular interest were the chest x ray and laboratory findings Prior to the seizure the chest x ray showed increased hilar markings in both midlung regions and hyperillumination of the lower lung fields Nine days later at the height of the asthmatic seizure an irregular circumscribed density was seen in the right hilar

region extending into the midlung Eleven days later the density had almost completely absorbed leaving increased bronchovascular markings (Figure 19)

The following laboratory studies were most instructive A bronchoscopy was negative Mantoux tests in strengths from 1 10 000 to 1 100 tuberculin were negative Gastric cultures were negative for acid fast organisms There were no parasites ova or occult blood in the stools The blood count revealed a leukocytosis ranging from 11 000 to 20 000 with an eosinophilia ranging from 13 to 70 per cent The total eosinophil counts ranged from 154 000 to 160 000 cells per cu mm The nasal discharges revealed 8 per cent eosinophils The patient remained at Seton Hospital for two months and was discharged with a diagnosis of Loeffler's syndrome

The syndrome associated with Loeffler's name has been found in a number of diseases including infestations with various parasites fungi and higher bacteria the inhalation of plant pollen and other agents commonly found in an allergic condition so called Tropical Pulmonary Eosinophilia Some authorities are of the opinion that even in the presence of specific agents such as those mentioned the mechanism is essen-

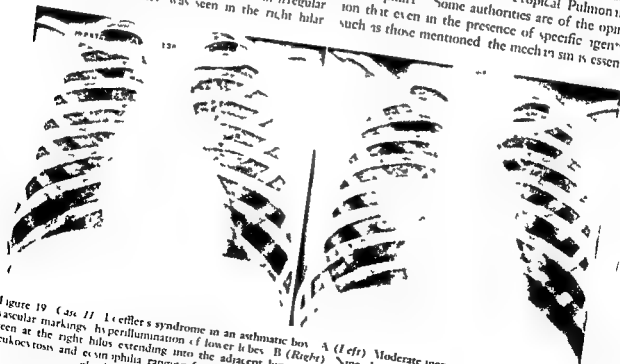


Figure 19. Loeffler's syndrome in an asthmatic boy. A (Left) Moderate increase in hilar and bronchovascular markings, hyperillumination of lower lobes. B (Right) Nine days later, an irregular density is now seen at the right hilus extending into the adjacent lung field. C (Center) Eleven days after B, the density had almost completely disappeared, leaving exaggerated hilar and bronchovascular markings.

tially allergic in nature since transient pulmonary infiltrations have been produced experimentally by parenteral injection of extracts of these agents in sensitized animals. Furthermore, these pulmonary infiltrations have been found to disappear temporarily after injection of epinephrin.

Loeffler's syndrome may be encountered in children as well as in adults. Schechter and Graub reported the condition in twins two years of age. Instances of Loeffler's syndrome have been described in association with various visceral involvements including that of the liver, stomach and other organs.

Zuelzer and Apt draw attention to the fact that, in contrast to the picture of Loeffler's syndrome in adults in which there is eosinophilia and leucocytosis of usually moderate degree and with predominantly pulmonary localization, in young children, the process is likely to affect the liver and is apt to be associated with a greater disturbance in the blood picture. Engfeldt and Zetterstrom also consider disseminated visceral lesions, associated with extreme eosinophilia, another facet of polyarteritis nodosa, featured by allergic granulomatoses and necrotizing lesions. They call the syndrome, 'Disseminated Eosinophilic Collagen Disease' (see Chapter 6).

In the differential diagnosis of Loeffler's syndrome, it should be mentioned that many individuals are currently being treated with sulfonamides, penicillin, streptomycin, liver injections and other drugs which are allergizing agents and often associated with eosinophilia. An intercurrent atypical pneumonia, during treatment of a patient receiving such medication, may be mistaken for Loeffler's syndrome. I have been puzzled by several such experiences.

That the pulmonary infiltrations in Loeffler's syndrome represent, in most cases, areas of eosinophilic pneumonia is substantiated by a number of reports describing the disease in patients who died accidentally. In four cases Meyenburg found the lungs to contain eosinophilic leucocytes and giant cell infiltration, marked interstitial proliferation and serous exudation. This investigator also noted minute granulomata and vascular alterations, the significance of which will become apparent later in discussions of rheumatic

pneumonia and polyarteritis nodosa. It should be noted, however, that Viswanathan suspects that the cases reported by Meyenburg may have been instances of tropical pulmonary eosinophilia.

A case, with autopsy findings reported by Bayley and co-workers revealed lesions consisting of pneumonic exudate containing large numbers of eosinophils. These investigators were impressed with the advanced stage of organization of the exudate, the presence of small granulomatous lesions and the occurrences of necrotizing arteritis and phlebitis. Fibrinoid swelling and necrosis of collagen were very prominent features and suggested an allergic basis. One gathers from these observations as well as those of Harkavy, Bergstrand and others, that even in presumably benign forms of Loeffler's syndrome the tissues may sustain vascular damage.

As a rule, eosinophilic pulmonary infiltrations of the type described cause minor complaints consisting of cough, headache, low grade fever and other catarrhal symptoms. Often there are no complaints at other times, as in the case previously cited, the symptoms are hyperacute and in a few, the course is protracted. The physical signs in the chest, if present, are minimal and non-informative of the true nature of the disease. The appearance of the chest x-ray, especially serial x-rays, and the finding of eosinophils in the blood, are decisive in diagnosis. The lungs reveal irregular densities of a soft appearance either

may take a week or several weeks, usually less than a month. A pleural effusion may be present. In some cases the chest x-rays show massive involvement. Upper lobe infiltrations, persisting for several weeks or months, may simulate tuberculosis. In fact, Loeffler in his original description of the condition, considered tuberculosis in the differential diagnosis. Lower lobe infiltrations simulate atypical or viral pneumonia. In a case reported by Elkeles and Butler, a transient apical cavity was found in a young soldier. The presence of eosinophilia, the absence of acid fast organisms in the sputum and the later appearance of fleeting pulmonary infiltrations led the au-

thors to conclude that the cavity was probably an area of resolution in an eosinophilic lung.

A most instructive case was reported by Buckles and Lawless. A man of fifty nine was found to have a density in the right upper lobe suggestive of a carcinoma. The sputum and bronchoscopic aspirations revealed monilia albicans on culture also eosinophilia. Cells were found which were very suggestive of cancer cells. The blood count revealed 12 100 leukocytes with 43 per cent eosinophils. Because of the persistence of the mass and the finding of cells suspicious of carcinoma a pneumonectomy was done. The examinations of the specimen revealed tissue changes compatible with Loeffler's syndrome. The microscopic features were fibrosis with massive infiltrations by eosinophils also polyarteritis with eosinophilic granulomatous areas endothelial cell proliferation with giant cells and mononuclear cells. Later studies showed a gradual reduction in the leukocyte and eosinophil counts with a return to normal figures within three months of the operation.

The allergic nature of Loeffler's syndrome finds additional support in the response of the disease to hormonal treatment. The administration of ACTH or cortisone causes a rapid fall in circulating eosinophils and radiographic clearing of the pulmonary infiltrations. Harkavy reported four cases of hyperergic vascular disease characterized by extensive purpura pulmonary infiltrations with eosinophilic myocarditis hepatosplenomegaly and renal involvement. Treatment with cortisone and ACTH was effective in controlling the reversible phases of the disease such as eosinophilic pulmonary infiltrations purpura joint pains and fever. It failed to halt the irreversible lesions in the heart and kidneys. Similar experiences of the striking beneficial effects of cortisone and ACTH in the treatment of Loeffler's syndrome have been reported by others.

SEVERE FORMS OF PULMONARY INFILTRATIONS AND EOSINOPHILIA

The patients in this group are more acutely ill and for longer periods. They usually have more extensive pulmonary involvement often compli-

cated by pleural and pericardial effusions. The patients are more apt to show hyperergic manifestations in other organs and evidence of polyarteritis on histological examination of tissues. The accompanying eosinophilia is usually more pronounced although in some the hematological findings are remarkably inconspicuous. The acute symptoms as well as the reversible elements of the pathological process are often controlled by ACTH or cortisone treatment.

Harkavy has stressed the importance of vascular allergy in the pathogenesis of bronchial asthma associated with recurrent pulmonary infiltrations and eosinophilic polyserositis. Since 1941 his thesis has been that not only the bronchi and other parts of the lungs may be involved in vascular reactions but also the myocardium serous membranes joints skin nervous and hemopoietic systems. These syndromes are determined by the number character and variations in the combinations of the shock tissues affected. Thus there may be a pulmonary myocardial pleuropulmonary myocardial or a pleuropulmonary myocardial response the latter resulting in some cases in a picture of constrictive pericarditis. With the extension of the process to all the serous membranes the characteristic symptoms of polyserositis appear. In the presence of these fundamentally allergic responses disturbances in the dynamic aspects of the circulation are inevitable. Although these symptoms Harkavy emphasizes that they are not of independent origin but are merely varying expressions of a state of hypersensitivity.

The more severe forms of hyperergic diseases which fall into Harkavy's group of patients have been documented under various titles such as Loeffler's Syndrome with Associated Eosinophilic Pleuritis Eosinophilic Pleural Effusion and Pericarditis with Effusion in an Allergic Subject and Transient Periods of Cardiac Enlargement Associated with Hypersensitivity to Different Etiologic Agents. In addition to reports such as those mentioned it is noteworthy that in a number of cases of so called acute primary or idiopathic pericarditis the authors draw attention to the frequent coexistence and

occasionally recurrence of pulmonary and pleural lesions. At times one even obtains an allergic history and an excess of eosinophils in the blood. It is suspected that in some instances idiopathic pericarditis is a manifestation of allergy representing a hypersensitive response of the pericardium to an upper respiratory tract infection (idiopathic pericarditis is a benign often recurrent disease frequently associated with effusions in other serous membranes). Moehlig and Steinbach stress the possible role of the adrenal cortex in causing peritoneal, pleural and pericardial effusions by interfering with water and electrolyte metabolism.

The course of the disease in the following patient illustrates graphically the thesis under discussion. In slightly over a year a man of thirty-seven developed five seizures of pulmonary infiltrations, pleuritis and/or pericarditis. The pleural fluid as well as the peripheral blood showed a preponderance of eosinophilic leukocytes. The acute febrile seizures were accompanied by chest pain, a pericardial friction rub and electrocardiographic evidence of pericarditis. Improvement followed ACTH and cortisone treatment.

Case 12. Male—Age 37

A dejected alcoholic stammerer had been afflicted since childhood with petit mal, sinus trouble, dizziness, tinnitus and abdominal pain. In June 1950 he was admitted to a hospital with cough, expectoration, chills, fever and left-sided chest pain. A chest x-ray revealed cardiac enlargement and infiltrations in both lower lung fields. There were healed fractures of a number of ribs. The patient improved and was discharged with a diagnosis of left lower lobe pneumonia, pleuritis and an enlarged heart. In August 1950 the patient had a recurrence of chest pain, cough and fever. He was rehospitalized and again there were found cardiac enlargement and densities in both lower lung fields. A chest x-ray taken three weeks later showed a decrease in the size of the heart and practically clear lung fields.

In September 1950, November 1950 and February 1951 the patient was treated for chest pain, fever and dyspnea. On each occasion the heart was found enlarged and infiltrations were present in both lower lobes, regressing in about three weeks.

On May 16, 1951 the patient consulted me for a recurrence of the seizure. The heart was enlarged, sounds distant, no murmurs, there was a diastolic gallop and a distinct pericardial friction rub heard. Blood pressure was 100/60. The chest x-ray showed cardiac enlargement. The patient was referred to the Montefiore Hospital for further study. A chest x-ray taken shortly after admission revealed irregular soft infiltrations in the left lower lobe and fluid at both bases. The heart appeared slightly smaller than in the film taken five days previously. In a short time the chest x-ray findings were within normal limits (Figure 20).

Repeated blood counts, chemical and serological tests, sputum examinations and blood cultures did not contribute significant information. The only positive finding was a rapid blood sedimentation rate. A bronchoscopy done on June 1, 1951 revealed the right main bronchus and subdivisions normal; the left lower bronchus appeared inflamed and narrowed. The patient ran a low grade fever and continued to complain of chest pain. He improved under crystallin and sedation. But soon the symptoms recurred and again the chest x-ray showed cardiac enlargement and linear infiltrations in both lower lung fields, also fluid at both bases.

A right thoracentesis yielded 20 cc of thick brown fluid containing 10 per cent eosinophils and large mononuclear cells. The fluid was sterile on culture. Blood examination revealed the hemoglobin 11 gm, red blood cells 3,900,000, white blood cells 9,000 with 62 per cent neutrophils, 19 per cent lymphocytes, 7 per cent monocytes and 12 per cent eosinophils. The sedimentation rate continued rapid. Examination of nasal secretion and sputum showed no eosinophils. The bone marrow showed a mild increase in eosinophils. Total eosinophil counts of the peripheral blood revealed a variation ranging from 737 to 967 cells per cu mm. There were no parasites in the stool. A tuberculin test was strongly positive in 1:1,000 dilution. OT, histoplasmin, skin test negative; trichinella skin test transiently positive; trichinella precipitin test negative. A muscle biopsy showed normal muscle.

Because of the persistent, fever, moderately high eosinophil count and continued symptoms, ACTH was started in doses of 15 mgm every six hours and continued for seven days. There was rapid improvement. The heart and lungs returned to a normal state; the eosinophil count fell to 44 cells per cu mm; the sedimentation rate returned to normal; slowly and the electrocardiogram which had previ-

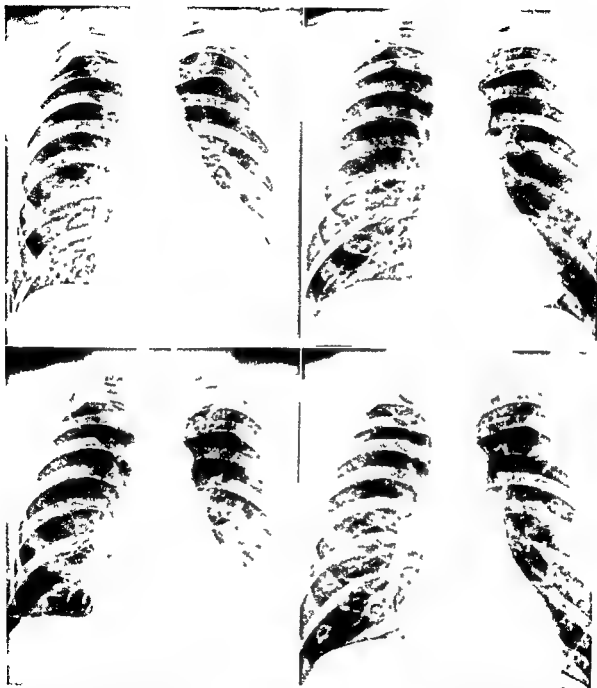


Figure 20 Case 12 Recurring pulmonary infiltrations pleuritis and pericarditis with eosinophilia A (Upper left) Circumscribed oval density in right lower lobe irregular infiltrations and pleural reaction left lower lobe heart enlarged evidence of healed rib fractures on left B (Upper right) Three weeks later regression of pleuropulmonary lesions decrease in size of heart C (Lower left) Three months later reappearance of pleuropulmonary lesions at left base linear striations at right base heart again enlarged D (Lower right) Two weeks later regression of lesions and size of heart (Over a period of fourteen months, five seizures occurred of the type shown clinical and electrocardiographic evidence of recurring pericarditis fluid aspirated from both pleural cavities showed an eosinophile count as high as 12 per cent increase in eosinophils in bone marrow smear and blood favorable response to ACTH and cortisone treatment)

ously revealed precordial T wave changes, consistent with the presence of pericarditis, resumed a normal pattern

On July 1, 1951 the patient had a recurrence of chest pain, fever and tachycardia. Chest x rays revealed cardiac enlargement and a left sided pleural effusion. The sedimentation rate increased and the leukocyte count rose to 15,000 with 1 per cent eosinophils. A left thoracentesis revealed 300 cc of yellow fluid which was sterile and contained rare eosinophils. Examination of the fluid as well as the peripheral blood for lupus cells was negative. By July 16, 1951 the heart resumed its normal configuration and the pleural effusion absorbed. The patient had mild chest pain and felt weak. He was again treated with ACTH, 15 mgm every six hours and gradually increased to 25 mgm every six hours. Following this there was steady improvement and gain in weight. The eosinophil count throughout this period ranged between twenty two to sixty six cells per cu mm. The patient was then placed on a maintenance dose of cortisone 25 mgms four times a day and the medication gradually curtailed. Chest x rays in October and November, 1951 showed no new developments.

TROPICAL PULMONARY EOSINOPHILIA

In 1940, Frimodt Muller and Barton studied 600 cases in a tuberculosis sanatorium in India in whom an eosinophilia of over 20 per cent was present. They found 175 who not only had eosinophilia but also unusual chest x ray findings which were not characteristic of tuberculosis. They termed the condition "Pseudo tuberculosis of the Lung, with Massive Eosinophilia." Three years later Weingarten encountered a similar condition in Bombay, India. He designated the disease "Tropical Eosinophilia" to which Ball later added the descriptive, "pulmonary," to indicate the major recognizable seat of the disease. Tropical pulmonary eosinophilia has been described under several other titles. Viswanathan, an early student of the disease reported in 1948 observations on 207 cases the majority were army personnel stationed in Assam and Burma. He also summarized the findings of 685 cases recorded in the literature.

Tropical pulmonary eosinophilia has been encountered mainly in India and Ceylon but a sizable number have been reported from other

tropical parts of the world, including the East Indies, Africa, China, Australia and the South West Pacific Islands. Sporadic cases have been studied in various parts of Europe and in the United States usually of Army personnel recently stationed in the aforementioned parts of the world.

Tropical pulmonary eosinophilia may pursue an acute or chronic course, in the vast majority, the latter. Viswanathan subdivides the acute type of disease into a self-limiting variety, in which the condition clears up quickly without treatment, and a variety which goes on to chronicity if left untreated. The acute type is featured by a sudden onset with high fever, cough and signs of an acute bronchitis or pneumonia. The chronic type is featured by general malaise, lassitude, low grade fever, later cough and periodic seizures of dyspnea which in some cases simulate asthma like paroxysms. The chest x-ray reveals mottled infiltrations chiefly at the lung bases. The hilar markings are apt to be prominent. The disease may be limited to a lobe or a lung or the distribution may be of a miliary type. In the chronic stages of the disease, only prominent bronchovascular markings may be seen. As pointed out by Westwood and Levine, almost any pulmonary shadow may be a manifestation of the eosinophilic lung syndrome.

Various theories have been suggested to explain the cause of tropical pulmonary eosinophilia. The fact that a high percentage of cases have positive serologic tests for syphilis is suggestive to some that the disease may be caused by a spirochete. The possibility that the disease is caused by a parasite appeals to others because mites have been isolated from the respiratory tract of some patients. The mites belong to various genera: *Tarsonemus*, *Tyroglyphus*, *Glyciphagus* and *Carpoglyphus*. Carter, Wedd and D'Abreu examined the sputa of twenty eight patients suffering from respiratory complaints. Various types of mites were demonstrable in the sputa of seventeen of the twenty-eight patients. In addition, there was an eosinophilia in the blood ranging from 6 to 66 per cent. Soysal and Javawardena reported thirty instances of transient pulmonary infiltrations in Ceylonese sol-

ders. The eosinophils in the blood ranged from 33 to 81 per cent. Mites of either *Tyroglyphus* or *Tarsonemus* were recovered from eleven sputum specimens of twenty-one cases examined. In a study of eight cases, Van der Sar was able to demonstrate mites in the sputum of each, confirming the studies of others that the condition may be a form of pulmonary acariasis. Coutinho considers the disease a distinct entity, probably caused by an infectious agent.

Pulmonary infiltrations associated with eosinophilia have also been encountered in individuals infested with other parasites including *Entamoeba histolytica*, liver flukes, trichinella and *Strongyloides intestinalis*. The condition has been observed in association with brucellosis, coccidioidomycosis and filariasis, a frequent cause of transient pulmonary infiltrations and eosinophilia, encountered in the southeastern coastal regions of the United States, is creeping eruption or cutaneous helminthiasis.

Tropical pulmonary eosinophilia is often indistinguishable from Loeffler's syndrome. In fact, some writers believe that the two are synonymous. Loeffler's original description referred to a type E possessing features resembling those of tropical pulmonary eosinophilia. Physicians who believe that Loeffler's syndrome and tropical pulmonary eosinophilia represent different diseases are impressed with the more protracted course of the latter, the presence of an enlarged

spleen, the high incidence of positive serological tests for syphilis, positive cold agglutinins, the demonstration of parasites in the sputum or stools and the response to treatment with arsenic. Tropical pulmonary eosinophilia responds, often dramatically, to organic arsenic given by mouth (Carbarsone) or intravenously (neocarsphenamine). Treatment with corticotropin has been found to exert transitory improvement. However, Sanjivi and co-workers are sufficiently impressed with the beneficial effects of ACTH and cortisone to conclude that tropical eosinophilia is a collagen disease or a state of allergy.

A scarcity of autopsy material has hampered a definitive understanding of the nature of tropical pulmonary eosinophilia. An unusual instance of chronic eosinophilia in a two year old Negro boy in whom the disease was associated with reversible necrosis of the liver confirmed by exploratory laparotomy on two occasions, also pulmonary infiltrations, anemia and ascaris infestation, impressed Perlingero and Gyorgy with the possibility that the pulmonary infiltrations and eosinophilia as well as the liver involvement found in the child, could be explained on the basis of an allergic response to ascariis toxin. But, in a careful study of four children with similar hepatic and pulmonary findings, Zuelzer and Apt concluded that the evidence was equally strong that the disease represented an unusual form of Loeffler's syndrome.

ISSUE CHANCES IN ALLERGY

BRONCHIAL ASTHMA

Bibliography

- BLOOM, H. G. A Classification of the Allergic Issue. *Responses New York State J. Med.* 51: 46, 1951.
- BROWN, E. A. Drug Allergy. *Quart. Rev. Allergy & Asthma* 1: 1, 1951.
- BROWN, J. A. Problems of Drug Allergy. *J. All. & Asthma* 8: 814, 1955.
- BUTLER, S. S. Correlation of Clinical and Autopsy Findings in 170 Cases of Asthma. *J. Allergy* 22: 191, 1957.
- COCK, A. F., and COHEN, R. A. On the Classification of the Phenomena of Hypersensitivity. *J. Immunol.* 8: 161, 1951.
- CURT, C. F. The Mechanism of Anaphylactic and Allergic Reactions. *Ann. Allergy* 14: 1, 1954.
- CROW, M. B. Bronchial Asthma. Classification Based on Etiological and Pathological Factors. *Ann. Int. Med.* 29: 590, 1944.
- DAIR, H. H. On Some Chemical Factors in Control of the Circulation. *Brit. M. J.* 1: 1093, 1949.
- DAIR, H. H., and LAIBLOW, P. P. The Physiological Action of β -Iminazolinethiazine. *J. Physiol.* 41: 318, 1910.
- FEIGER, A. M. Eosinophilia. *N. Y. J. Med.* 51: 1681, 1953.
- HARRIS, T. N., GARNER, L., MERRITT, F., and FINKEL, W. E. The Role of the Lysingocyte in Anaphylactoid Formation. *Exper. Med.* 21: 73, 1945.
- KATZ, R. L. *Tissue Immunity*. Springfield, Illinois, Charles C. Thomas, Publisher, 1946.
- KATZ, B. S. Tissue Changes in Allergy. *J. Allergy* 19: 10, 1948.
- KNOTT, J. M., and GIBBERT, R. A. Radioallergic Diagnosis of Eosinophilia. *Lab. Invest.* 12: 1, 1951.
- LANDSTEINER, K. Experiments on Anaphylaxis to Antigen. *J. Exper. Med.* 29: 611, 1944.
- LEWIS, F. The Blood Vessels of the Human Skin and Their Responses. *London Slun & Sons, Ltd.* 1937.

- MELTZER, J. J. Bronchial Asthma as a Phenomenon of Anaphylaxis *J A M A*, 55 1021, 1910
- PIROUET, C. von Allergie *Munchen med Wchnscr*, 53 1457, 1906
- PIROUET, C. von, and SCHICK, B. Die Serumkrankheit Wien, F. Deuticke, 1905
- PRICKMAN, L. F. General Principles of Allergy and Hypersensitivity *Proc Staff Meet, Mayo Clin*, 24 429, 1949
- RACKEMANN, F. M. A Working Classification of Asthma *Am J Med*, 3 601, 1947
- SANJIVI, K. S., THIRUVENKADAM, K. V., and FRIEDMANN, H. C. Tropical Eosinophilia Treated with Cortisone *Dis Chest*, 28 76, 1955
- SANJIVI, K. S., THIRUVENKADAM, K. V., and FRIEDMANN, H. C. Tropical Eosinophilia Treated with Cortisone *Dis Chest*, 28 88, 1955
- SCHILD, H. O. HAWKINS, D. F., MONGAR, J. L., and HERZ HEINER, H. Reactions of Isolated Human Asthmatic Lung and Bronchial Tissue to a Specific Antigen *Lancet*, 2 176, 1951
- SELVE, H. The Alarm Reaction and the Diseases of Adaptation *Ann Int Med*, 29 403, 1948
- URBACH, E. *Allergy* New York, Grune and Stratton 1943
- WALZER, I. and FROST, T. T. Death Occurring in Bronchial Asthma. A Report of Five Cases *J Allergy* 23 204, 1952
- WILLIAMS, H. L. A Phylogenetic Concept of Allergy *Proc Staff Meet, Mayo Clin*, 24 516, 1949
- WINTER, B. M., BEAKEY, J. F., and SEGAL, M. S. A Clinicopathologic Study of Bronchial Asthma with Consideration of its Relationship to the General Adaptation Syndrome *Ann Int Med*, 33 134, 1950
- WINTROBE, M. M. *Clinical Hematology* 3rd ed Philadelphia Lea and Febiger, 1951 p. 214
- ### PULMONARY INFILTRATIONS AND EOSINOPHILIA
- BALL, J. D. Tropical Pulmonary Eosinophilia *Tr Roy Soc Trop Med & Hyg*, 44 237, 1950
- BAYLEY, E. C., LINDBERG, D. O. N., and BAGGENSTOSS, A. H. Loeffler's Syndrome. Report of a Case with Pathologic Examination of the Lungs *Arch Path*, 40 376, 1945
- BLANTON, H. W. Observations on Loeffler's Syndrome. Report of 4 Cases *Virginia M Month*, 72 473, 1945
- BUCALES, M. G. and LAWLESS, E. C. Pneumonecrosis in a Case of Loeffler's Syndrome *Dis Chest*, 18 313, 1950
- CARTER, H. F., WERN, G., and D'ABREDA, V. S. E. Occurrence of Mites (Acarina) in Human Sputum and their Possible Significance *Indian M Gaz*, 79 163, 1944
- COUTINHO, A. Tropical Eosinophilia *Ann Int Med*, 44 88, 1956
- CROFTON, J. W., LIVINGSTONE, J. L., OSWALD, N. C., and ROBERTS, A. T. M. Pulmonary Eosinophilia *Thorax*, 7 1, 1952
- DIAS RIVERA, R. S., RAMOS-MORDES, F., and CINTRON RIVERA, A. Infiltrative Eosinophilia *Arch Int Med*, 94 102, 1954
- DICKIE, H. A., and GRIMM, E. Loeffler's Syndrome with Associated Eosinophilic Polyserositis *Am J Med*, 7 690, 1949
- EKELER, A., and BUTLER, N. R. Transitory Pulmonary Infiltrations and Apical Cavitation Associated with Eosinophilia *Brit J Radiol*, 19 512, 1946
- ENGELFELDT, B., and ZETTERSTROM, R. Disseminated Eosinophilic Collagen Disease *Acta med Scandinav*, 153 337, 1956
- FEDER, I. A., HOFFMAN, J., and SUGAR, H. Acute Primary Pericarditis *Am J M Sc*, 220 144, 1950
- FELDMOT MOLLER, C., and BARTON, R. M. Pseudo tuberculous Condition Associated with Eosinophilia *Indian M Gaz*, 75 607, 1940
- GILLEY, C. W., MCCORD, M. C., and TAGUCHI, J. T. Acute Nonspecific Pericarditis *Am J M Sc*, 222 249, 1951
- HANI, J. C., and ZAVIDAR, W. T. Loeffler's Syndrome and Pulmonary Infiltrations Accompanied by Peripheral Eosinophilia *Ann Int Med*, 29 468, 1948
- HARRAVY, J. Cardiovascular Allergy due to Penicillin, Sulfadiazine, and Bacterial Sensitization *J Allergy*, 23 104, 1952
- HARRAVY, J. Vascular Allergy. Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis *Arch Int Med*, 67 709, 1941
- HERBERT, P. DE VRIES, J. A., and ROSE, B. Studies on Effect of Administration of Pituitary Adrenocorticotrophic Hormone (ACTH) to Case of Loeffler's Syndrome and Case of Tropical Eosinophilia *J Allergy*, 21 12, 1950
- IRWIN, J. W. Tropical Eosinophilia *Ann Int Med*, 25 329, 1946
- KARAN, A. A., and SINGER, E. Transitory Pulmonary Infiltrations Mistaken for Tuberculosis with a Report of Five Cases *Ann Int Med*, 47 106, 1942
- KARTGENER, M. Das chronische Lungeninfiltrat mit Eosinophilie *Schwed med Wchnscr*, 72 862, 1942
- LOEFFLER, W. Zur Differential Diagnose der Lungeninfiltrationen II. Über flüchtige Sucedan Infiltrate (mit Eosinophilie) *Beitr Klin Tuberk*, 79 358, 1937
- MARR, L. Loeffler's Syndrome with a Report of Twenty Three Cases *Dis Chest*, 25 128, 1954
- MCKINLAY, C. A. Allergic Carditis, Pericarditis and Pleurisy *J Lancet*, 68 61, 1948
- MCKINLAY, C. A. Transient Periods of Cardiac Enlargement Associated with Hypersensitivity to Different Etiologic Agents. Report of a Case *Ann Int Med*, 35 256, 1951
- MOESLING, R. C., and STEINBACH, A. J. Role of the Adrenal Cortex in Certain Peritoneal, Pleural and Pericardial Effusions *J Michigan M Soc*, 50 174, 1951
- PERLINGIERO, J. G., and GYORGY, P. Chronic Eosinophilia. *Am J Dis Child*, 73 34, 1947.
- ROBERTSON, R. F. Pleural Eosinophilia *Brit J Tuberc & Dis Chest*, 48 111, 1954
- SCHREIBER, F. R., and GRAUB, M. Loeffler's Syndrome *J A M A*, 146 1420, 1951
- SLOWEN, J. F. A Case of Transient Successive Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichinosis *Ann Int Med*, 21 130, 1944
- SMALLEY, R. F., and REDDOCK, J. C. Acute Pericarditis. A Study of Eighteen Cases Among Service Personnel *Ann Int Med*, 25 799, 1946
- SOUSA, E., and JAYAWARDENA, M. D. S. Pulmonary Acarosis. A Possible Cause of Asthma *Brit M J*, 1 1 1951
- VAN DER SAR, A. Pulmonary Acarosis *Ann Rev Tuberc*, 53 440, 1946

- VINCENT, R. Pulmonary Eosinophilosis. *Quart J Med.*, 17:257, 1948
- VON MEYERBURG, H. Das eosinophile Lungeninfiltrat. *Pathologische Anatomie und Pathogenese. Sitzber. med. W. d. Gesellsch.*, 72:809, 1942
- WEINGARTEN, R. J. Tropical Eosinophilias. *Lancet*, 1:103, 1943
- WINTHROP, L. A., and LEVY, S. The Eosinophilic Lung. *Tubercle*, 32:98, 1951
- WRIGHT, D. O., and GOLD, E. M. Löffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis). *Arch. Int. Med.*, 75:301, 1945
- ZIMTZ, N., and OSTLAC, J. V. Eosinophilic Pleural Effusion and Pericarditis with Effusion in an Allergic Subject. *J. Allergy*, 20:136, 1949
- ZULLER, W. W., and APT, I. Disseminated Visceral Lesions Associated with Extreme Eosinophilia. *Am. J. Dis. Child.*, 78:153, 1949

Allergic Diseases (Concluded)

The "Collagen" Diseases

A HETEROGENEOUS group of conditions have been linked together under the term, "collagen" diseases. These entities are probably of diverse origin in spite of the fact that they possess common histological features as well as merging clinical patterns. Strictly speaking, the collagen diseases include *polyarteritis nodosa*, acute disseminated lupus erythematosus, scleroderma and dermatomyositis. In the course of time, additional entities have been incorporated, including erythema nodosum, rheumatic fever, rheumatoid arthritis, serum sickness, drug sensitization, blood incompatibility in transfusions, acute glomerulonephritis and several others. It is well to emphasize, however, that the mere fact that the collagen diseases share certain morphological features does not necessarily imply a common cause, in fact, there are many reasons, clinical as well as experimental, to minimize the significance of this 'catch-all term for maladies with puzzling clinical and anatomical features' (Klemperer). For the sake of convenience only, the collagen diseases which are traditionally associated with skin changes (disseminated lupus erythematosus, scleroderma and dermatomyositis) will be discussed in the section dealing with diseases of the skin.

The pathological changes in the collagen diseases involve the connective tissue or the filler between the cellular elements of the body. The connective tissue is composed of fibers and interfibrillar substance. The substance is derived from mesenchyme, the progenitor of smooth muscle, endothelium and mesothelium. Hence the close relationship existing between the several conditions mentioned previously, also the predilection of the collagen diseases for blood vessels and

serous membranes. Various aspects relating to the pathological changes will be discussed in conjunction with descriptions of individual conditions. For the group as a whole, Calkins and Bauer summarize the pathological features of connective tissue diseases as follows:

In the initial stages there is an accumulation of a jelly like, stainable matrix consisting of mucopolysaccharides, water and other components. The swelling and loosening of the structure of the collagen is associated with the exudative phase of the disease. There may or may not be an accompanying fibrinoid reaction in the form of masses of eosinophilic, homogeneous or finely granular material. Around the area of the greatest tissue damage, especially around proliferating blood vessels, there is invasion and proliferation of lymphocytes, polymorphonuclear leukocytes, monocytes, eosinophils and plasma cells. In time, there is fibroblastic proliferation eventually replaced with scar formation. With the exception of fibrinosis and the relatively slow evolution of the process, the pathologic features of connective tissue diseases are similar to those of wound healing.

INTERRELATIONSHIP OF THE 'COLLAGEN' DISEASES

As a matter of historical interest, it is noteworthy that for many years pathologists had drawn attention to the presence of arterial lesions suggestive of *polyarteritis nodosa* in the tissues of patients with rheumatic fever. Others had stressed the fact that in a significant number of patients articular and cutaneous lesions are en-

countered in polyarteritis nodosa as well as in rheumatic heart disease. Friedberg and Gross described four cases in which the postmortem examination revealed widespread arterial lesions in association with rheumatic fever and rheumatic heart disease the latter confirmed by the presence of Aschoff bodies in the myocardium. In the early phases of acute disseminated lupus erythematosus and acute dermatomyositis the diagnosis is often acute rheumatic fever or rheumatoid arthritis. Later sections will deal with various problems concerned in differential diagnosis. A striking example of the interrelationship sometimes found between various collagen diseases was recently cited by Garland and Sisson. A patient, male, aged forty, with rheumatoid arthritis died shortly after examination. The autopsy disclosed diffuse collagen disease with (a) polyserositis (peritoneal, pleural and pericardial fluid), (b) rheumatic heart disease (aortic valve stenosis, c) "wire looping" of renal glomeruli (as in lupus erythematosus), (d) rheumatoid arthritis and (e) polyarteritis nodosa involving the pulmonary, thyroid and testicular arteries. The close relationship between the aforementioned conditions is supported by the work of Rich and Gregory who showed that the basic pathological features of rheumatic carditis and arteritis can be produced by causing "serum sickness" in rabbits. These investigators also showed that anaphylactic pneumonia, caused by hypersensitivity in man, has the basic characteristics of rheumatic pneumonia. It should be mentioned that some years previously Fried demonstrated allergic inflammation of the lungs by means of repeated injections of horse serum into rabbits. The microscopic examination of the pulmonary tissues showed in some instances a preponderance of eosinophilic cells, necrosis of blood vessels resembling "arteritis nodosa" and cellular infiltration producing a condition resembling granuloma.

Polyarteritis Nodosa with Pulmonary Involvement

In 1866, Kussmaul and Maier described the gross and microscopic appearances of a disease which they named periarthritis nodosa. With the later recognition that the changes affect all coats of small and medium sized arteries the more descriptive term polyarteritis nodosa came into general use. In hypersensitivity reactions one of the variants of the disease small blood vessels of any type, including capillaries and venules may be involved.

The changes in polyarteritis nodosa affect initially the media of the muscular arteries which becomes necrotic and edematous. There is early involvement of the entire vessel wall with infiltration of cellular elements chiefly eosinophilic leukocytes. As a result of weakening of the vessel wall, small aneurysmal dilations develop causing nodular changes along blood vessels hence the original name. The inflammatory process soon extends to the perivascular stroma. Intracavitary thromboses develop and this is followed by fibrous replacement and occlusion of the lumina of the affected vessels. Recanaliza-

tion of thrombi often occurs. The weakened wall which has undergone aneurysmal dilatation may rupture and lead to hemorrhage. The occluded arteries cause infarction of the tissues supplied. The perivascular changes, appearing grossly as nodules of varying size along blood vessels, are found chiefly in the kidneys, heart, liver, skeletal muscles and nervous system. Increasing attention is lately being paid to the vascular changes in the lungs.

PATHOGENESIS

In recent years studies of polyarteritis nodosa have concerned themselves chiefly with the etiology of the disease and the clinical signs which may permit a diagnosis during life. In 1925, Gruber postulated that polyarteritis nodosa is a manifestation of hypersensitivity and that the condition may be caused by a variety of infectious and toxic agents acting on blood vessel walls. This view is supported by the frequency with which bronchial asthma, eosinophilia and other allergic manifestations are found in association with the condition. Additional support is

offered by the studies of Rich and Gregory who noted focal arterial lesions in tissues after experimental induction of "serum sickness" in animals and after sulfonamide hypersensitivity. But, inasmuch as polyarteritis nodosa may develop in patients in whom an allergic background is not demonstrable, Zeek and others make a distinction between polyarteritis of the essential or classical type and of, so called, hypersensitivity angitis. Pulmonary vascular lesions are uncommon in polyarteritis nodosa of the essential type but they are frequently encountered in hypersensitivity angitis. Pulmonary lesions are also an integral part of a subtype known as Wegener's granulomatosis (allergic granulomatous angitis) to which reference will be made later.

Blankenhorn and Knowles draw attention to the fact that of late subgroups and bizarre forms of polyarteritis are being reported with increasing frequency since almost any tissue which has blood vessels may be the site of typical vascular lesions. The latter may be associated with almost any disease (disseminated lupus, dermatitis herpetiformis, rheumatoid diseases, sarcoidosis, Felty's, Reiter's, Wegener's and Cogan's syndromes). Furthermore many agents, exclusive of foreign serum and sulfonamides may also give rise to necrotizing angitides, including mercurial diuretics, penicillin, thiouracil and drugs producing purpura or hemolytic anemia.

CLINICAL FEATURES

As mentioned, for many years polyarteritis nodosa was of pathologic interest only, the disease rarely recognized during life. Currently, the disease is being diagnosed with increasing frequency not only when it involves the heart and kidneys, the sites of predilection, but also when it affects the lungs. It is beyond the scope of these pages to describe the variegated clinical facets of the disease except to mention that the illness is often acute, occasionally protracted, if the former, it is characterized by fever, chills and prostration. Localizing symptoms and signs are related to the nature of the organ or organs predominantly affected by the vascular changes. Involvement of the kidneys may present a picture of increasing renal insufficiency leading to

failure. Myocardial involvement may terminate in cardiac failure. Infarction of abdominal vessels and organs may give rise to symptoms and signs of acute mesenteric thrombosis. Involvement of the lungs may be reflected in atypical pneumonia. Obviously, when there is severe cardiorenal damage, a fatal issue is almost inevitable. But there is reason to believe that patients may survive if the disease is localized to organs such as the lungs possessing considerable functional reserve. In such, the disease may undergo arrest. Kleit reported two cases in which apparent recovery took place but in one the disease reappeared after a lapse of twelve years. Similar experiences of apparent recovery have been reported by others. The following case, under the writer's observation for the past eight years is an example of clinically arrested polyarteritis nodosa but in which the outlook for complete recovery is still in doubt. The course of the disease in this patient is in keeping with a hypersensitivity angitis.

Case 13 Male—Age 50

The patient, a tailor, had an allergic family and past personal history. On August 12 1946 he consulted his physician because of tingling pain and itching of the hands and a feeling of tightness of the shoulders. The face felt flushed and swollen. Physical examination revealed congestion and edema of the tufts of the fingers, also redness of the palms of the hands. There was definite edema about the eyelids. It was suspected that the patient had some form of angioneurotic edema and he was treated with an injection of 0.5 cc epinephrin and capsules of benadryl.

The patient returned to his physician six days later stating that he had gone back to work but that the swelling of the finger tips and itching prevented him from holding the sewing needle. He had also experienced pain in the joints of the hands, elbows, shoulders and knees as well as increasing shortness of breath. Examination now revealed a dyspneic man, tired looking, with swollen eyelids and swollen, painful joints. The temperature was 101.5°. On auscultation rales were heard over both lower lobes also altered breath sounds although the patient had no cough or expectoration. A chest x-ray taken four days later revealed irregular infiltrations in both lower lobes and a pleural reac-

tion at both bases. The cardiac contour suggested poor tone with a possible pericardial effusion (Figure 21A).

The patient was admitted to a hospital and treated for a week with penicillin and sulfadiazine. However, the fever, pain and finger swelling persisted but the edema of the face subsided gradually in the course of the following six weeks. Soon the swelling and itching of the face and hands recurred and there also appeared swelling of the tongue and marked elevation of temperature. The patient was then treated with streptomycin but this had to be discontinued because of hyperpnea and severe constitutional reactions.

The course of events following this episode was characterized by slight unproductive cough, remittent fever, swelling and vague pains in the joints and generalized malaise. The chest x-rays at first were in keeping with a bilateral bronchopneumonia and fluid at the bases. Repeated examinations of the sputum for acid fast organisms and fungi were negative. Cold agglutinins, blood cultures and biopsy of an epitrochlear lymph node were noninformative. Agglutination tests for the typhoid group of organisms were also negative. Significant findings were the presence of a relatively low leukocyte count ranging around 6,000 cells and continuing 4 to 6 per cent eosinophils, also a rapid blood sedimentation rate. A chest aspiration revealed an

exudate with a preponderance of eosinophilic leukocytes.

Since January, 1947, the patient has been seen by me several times a year. The course of events has been characterized by moderate cough, dyspnea on exertion, weakness of the hands and occasional eczematoid eruption with oozing and itching of the finger tips. On auscultation fine rales are always audible over both lower lungs. The blood sedimentation rate continues to be elevated. Serial chest x-rays have shown a decrease in the patchy infiltrations and absorption of the pleural exudate and in their place a diffuse interstitial fibrosis of a reticular character (Figure 21B). A muscle biopsy done in February, 1952 failed to reveal vascular lesions. A lung biopsy showed the pleura thickened, somewhat edematous with increased numbers of capillaries, also fibrous thickening of alveolar walls, increased vascularity and cellularity of interalveolar septa, also cellular infiltration around bronchi and into alveolar spaces, all mononuclear, also conspicuous thickening of the wall of small arteries.

Since vascular damage is the basic feature of the disease which may affect various organs of the body, it is understandable why polyarteritis nodosa may assume diverse clinical disguises. The evolution of the disease ranges from that of an acutely progressive and fatal illness, as even



Figure 21. Case 13
in both lower lobes
out both lungs, espe-
cially and progressive

plified in its 'classical' form, to a relatively indolent and localized granuloma. In a case of necrotizing angitis reported by Kampmeier and Shapiro, the patient showed over a span of twenty years evidence of dermatomyositis on one occasion, disseminated lupus erythematosus on another and polyarteritis nodosa on still a third. When the patient died the only evidence of the disease, demonstrable at autopsy, was in a section of hemorrhagic rectus abdominis muscle. Thickened small arteries were conspicuous in the heart, gallbladder, intestinal tract and kidneys.

The more important laboratory findings of polyarteritis nodosa include the presence of hypochromic anemia, leukocytosis, eosinophilia in the presence of bronchial asthma, an elevated blood sedimentation rate occasionally a false positive serology, albuminuria, hematuria and systemic hypertension indicative of renal damage and abnormal electrocardiographic tracings indicative of cardiac involvement. Of the greatest value is biopsy confirmation obtained from specimens of the skin or other tissues but such proof is available in only a small percentage of cases.

PULMONARY LESIONS

Polyarteritis nodosa in its classical form does not involve the blood vessels of the lungs as nearly as often as those of the kidneys, heart and other organs. When the lungs are involved the symptoms are apt to be overshadowed by the more profound disturbances caused by cardiovascular disease. More often symptoms referable to the respiratory tract are caused by congestive heart failure. Harris and co-workers found the lungs involved in 25 per cent of the cases and somewhat higher percentages of pulmonary involvement have been reported by others. Griffith and Vural noted that among seventeen patients with polyarteritis nodosa, in whom the diagnosis was confirmed at autopsy, in eight a clinical diagnosis was made of pneumonia, bronchopneumonia or pulmonary infarction. The majority complained of dyspnea, chest pain and cough. Liban and co-workers reported the case of a nine-month-old infant with polyarteritis nodosa. The lesions were in the healed or heal-

ing stage of the disease and confined predominantly to the lungs and heart. These authors state that about 110 cases of the disease have been reported in children under fifteen years of age. Of these, only ten cases have occurred during the first year of life.

The changes in the lungs resulting from polyarteritis nodosa partake much of the features characterizing the disease in other organs. The gross appearance of the organs may be quite deceptive. Only the histologic examination reveals the true nature of the disease. The most frequent findings are whitish nodules along the small arteries, particularly in the hilar region. Elman and Cudkovicz believe that the vascular occlusive changes are chiefly in the territory of the bronchial arteries and that the lung changes may represent the effects of progressive pulmonary ischemia resulting from the loss of a bronchial arterial blood supply. Braunstein points out that many of the reported cases are based entirely on clinical evidence. This investigator documented six cases of periaarteritis nodosa limited to the pulmonary circulation. In each instance there was also pulmonary hypertension, three of these being associated with mitral stenosis, one with congenital absence of the interatrial septum, one with multiple thrombotic occlusions of small pulmonary arteries and in one the pulmonary hypertension was of unknown etiology. In this localized form of arteritis, Braunstein found the pulmonary arteries chiefly affected. The cases reported in the literature of periaarteritis nodosa limited to the lungs have also occurred in patients with pulmonary hypertension. Bank studied forty-two cases in which the autopsy diagnosis was periaarteritis nodosa. He noted that in patients with malignant hypertension the lungs were rarely involved. On the other hand in a group with idiopathic periaarteritis the lungs were frequently involved.

As all noted that sections of lung may show a normal pulmonary artery lying adjacent to a diseased bronchial artery. Conversely, in rheumatic lungs the necrotizing arteritis, closely resembling polyarteritis nodosa, involves the pulmonary circulation to the exclusion of the systemic one. In the cases described by Banowitz, Polay and

Character the pulmonary arteries showed acute inflammatory infarcts extending to the pleural surface. The parenchymal lesions may be acute granulomatous or healed. The granulomatous lesions are characterized by giant cells of the Langhans type, macrophages and eosinophilic leukocytes. The infarcts secondary to arterial lesions may show various stages of healing large infarcts at times showing central cavitation.

There is a form of vascular disease so called Wegener's granulomatosis which is characterized by necrotizing granulomatous lesions of the upper as well as the lower respiratory tracts generalized arteritis and focal glomerulitis. The vascular involvement is chiefly of the small vessels which show acute and healing lesions in all stages. Renal lesions are a regular occurrence in Wegener's syndrome is generally considered a disease of hypersensitivity. In a detailed description of this disease Fahey and co workers reviewed twenty two cases reported in the literature chiefly in journals of pathology and added seven of their own. Wegener's granulomatosis although rare evinces a predilection for the respiratory tract.

I had occasion to follow the course of a Puerto Rican female age twenty three in whom the clinical and autopsy findings were in keeping with Wegener's syndrome. The patient had asthma since childhood. Five weeks prior to admission to Lebanon Hospital on June 22, 1953 she became ill with fever, cough and chest pain and on one occasion had bloody sputum. The patient was acutely ill, emaciated, very pale and complained of weakness, epigastric pain, pain in the forearms, back and ribs. The physical examination revealed rhonchi and crepitant rales through both lungs but no distinct evidence of consolidation. The chest x-ray revealed numerous small infiltrations in both lungs especially the bases. The spleen and liver were palpable. Various laboratory tests were done including blood cultures, blood chemical analyses and LE tests but all were noninformative. The blood count revealed severe anemia and leukocytosis with persistent eosinophilia of 18 to 38 per cent. The urine showed 4 plus albumin, red blood cells, white blood cells and casts. A skin biopsy re-

vealed one small unidentifiable granuloma but the significance of this finding was not fully appreciated until the post mortem examination.

The patient gradually developed increasing azotemia, edema of the face and sacrum. Late in the disease the patient developed pustular lesions around the nose and lips also ulcerative nodules on the forehead, upper lip, arms, elbows and buttocks. The patient received blood transfusions, penicillin, streptomycin, iodides, ACTH and cortisone but the course was relentlessly downhill and she expired on the 110th hospital day.

The autopsy performed by Dr J. C. Ehrlich revealed fresh ulcerations in the mucosa of the larynx, trachea and main bronchi. There were acute and chronic hemorrhages in the lungs. There was edema of the pulmonary septa and Wilson bodies were found. In addition there was disseminated necrotizing angitis with extravascular and necrotizing granulomas especially on the face, trachea, breasts, small intestine and spleen. There was diffuse glomerular involvement which caused the renal failure and uremia. There were several ulcers in the duodenum due to artery occlusion at the base of each ulcer. Parkin and co workers draw attention to the recurrent and severe pulmonary hemorrhages which may occur in the presence of necrotizing pulmonary alveolitis. In seven patients believed to have had hypersensitivity states as evidenced by glomerulonephritis in each instance and prominent clinical feature. Pathologically the pulmonary lesion was characterized by an acute necrotizing alveolitis which bore certain similarities to the pulmonary lesions described in hypersensitive animals and humans. It is noteworthy that the pathologic findings in Wegener's granulomatosis as detailed by Fahey and co workers, showed active and healed necrotizing inflammatory lesions in the form of infarcts, hemorrhages, thromboses and aneurysms. In fact in two cases hemoptysis was among the initial complaints. The cases described by Parkin and co workers resemble closely those reported showing Wegener's syndrome. In fact there is



in a patient with
irregular menses
and lower portions
two weeks later at
level C (Lower)
in the mitral heart
by synchrotron and
x-ray. A skin bi-
opsy with dermato-

1. The
 2. The
 3. The
 4. The
 5. The
 6. The
 7. The
 8. The
 9. The
 10. The

Rheumatic Pneumonia

Rheumatic pneumonia is believed to be an expression of hypersensitivity to a hemolytic streptococcal infection. In about 90 per cent of patients with rheumatic fever there is serologic evidence of a preceding infection with this organism as shown either in an elevation of the antistreptolysin-O titre or other tests for antibodies. Rheumatic pneumonia is not a clear cut pathological entity. By the time the lungs are examined at autopsy the organs are edematous congested and often the seat of extensive infarction. In fact, some investigators consider rheumatic pneumonia the result of a combination of rheumatism and congestive changes. In any event it is estimated that rheumatic pneumonia occurs in only about 5 per cent of patients with acute rheumatic disease. Rheumatic pneumonia is characterized histologically by thickening of alveolar walls and interstitial tissues, intraluminal exudates, hyaline membrane formation, vascular and perivascular lesions and on rare occasion Masson bodies, the counterpart of Aschoff bodies, which are small granulomas in alveolar ducts and alveoli.

The clinical features of rheumatic pneumonia vary widely depending on the nature of the rheumatic manifestations, the competency of the heart and the status of the pulmonary circulation. The pulmonary symptoms run the gamut from a mild respiratory infection with low grade fever, moderate cough and expectoration to a hyperacute disease with high fever, cyanosis, severe dyspnea, evidence of pulmonary edema and heart failure. In some the occurrence of rheumatic pneumonia hardly causes a demonstrable increase in symptoms. There is seldom a chill or sudden pain in the chest such as heralds most bacterial pneumonias. The physical findings are inconstant and nonuniform.

The roentgen features of rheumatic pneumonia are not associated with a sufficiently distinctive pattern to enable one to differentiate the condition from pulmonary congestion which usually coexists to some degree. In the absence of gross evidence of congestive heart failure, the appearance of patchy infiltrations in both lungs

particularly in the upper and midportions occurring early in the development of the rheumatic state is suggestive of rheumatic pneumonia. The pulmonary infiltrations may assume mulberry or nodular configuration. Inasmuch as bacterial pneumonias are seldom encountered in rheumatic fever, roentgen findings such as those mentioned, occurring in patients with active but not decompensated rheumatic heart disease should make one suspect rheumatic pneumonia. The course of the disease in the following patient, which was featured by a synchronous and progressive involvement of the heart and lungs, also the autopsy findings illustrate the more important features of rheumatic pneumonia.

Case 15 Female—Age 10

The patient was admitted to the Morrisania City Hospital on December 14, 1947, with a history of cough and fever of four days' duration. The girl appeared acutely ill, irritable and had constant cough occasionally productive of bloody sputum. The physical examination disclosed a loud systolic murmur at the apex and rales throughout the right lung. A chest x-ray revealed the heart moderately enlarged with flattening of the left border. There were no significant lesions in the lungs (Figure 74A).

For a time the patient improved but soon an exacerbation occurred, the temperature rose and the patient became increasingly dyspneic, orthopneic and cyanotic. On auscultation one could now elicit a gallop rhythm, frequent extrasystoles and the murmurs were more pronounced. The chest x-rays revealed the heart increased in size in all chambers and the lungs showed massive irregular densities involving chiefly the midthirds of both lungs (Figure 74B). There appeared increasing edema of the ankles and liver enlargement. Blood cultures were negative. On one occasion a non-hemolytic staphylococcus was found. Spinal fluid was negative. Urine showed albumin + plus and numerous red blood cells. Other laboratory examinations were noninformative. The girl went rapidly downhill with increasing evidence of heart failure and died July 11, 1949, approximately seven months after the acute onset of the disease.

The autopsy revealed no pleural adhesions. A



Figure 24 Case 15 Rheumatic pneumonia in a girl A (Left) Heart enlarged with flattening of left border lungs clear B (Right) Two weeks later fan shaped, fluffy densities radiating into the central zones of both lungs, marked increase in size of heart (Autopsy showed rheumatic endocarditis of mitral and tricuspid valves congestion and edema of lungs with thickening of septa and mononuclear cell permeation rheumatic pneumonia duration of illness seven months)

small amount of clear yellowish tinged fluid was present in each pleural cavity. The lungs were firm but crepitant and floated in water. They were patchy, dark and light red with grayish mottling and slightly edematous. The bronchi and pulmonary vessels were normal. The peribronchial nodes were soft and slightly enlarged. The heart was markedly hypertrophied and all chambers were dilated. The mitral ring was dilated, edges of cusps were thickened and verrucous at the coaptation of the border. Tricuspid was dilated with verrucae at the border. The left ventricle measures 15 mm in thickness the right ventricle 9 mm.

Microscopic examination revealed in the lungs the septa thickened by edema and numerous red

blood cells. The alveoli in scattered areas contained many mononuclear cells, some of the larger cells containing brown pigment. There was marked congestion. Within many of the alveoli edema was present. The heart revealed scattered areas of fibrinous collagen degeneration in the myocardium in which Aschoff cells, mononuclears and some polymorphonuclear cells were found. At the coaptation border of the mitral and tricuspid valves hyalinized nodules and verrucae were clearly seen. The diagnosis was rheumatic heart disease, enlarged heart, mitral insufficiency and tricuspid insufficiency, endocarditis, cerebral edema, ascites, hydrothorax, chronic passive congestion of liver and lung and rheumatic pneumonia.

Pulmonary Lesions in "Rheumatoid Disease"

"Rheumatoid disease," according to Ellman is a more descriptive term than rheumatoid arthritis because the former expresses a widespread process affecting not only the locomotor but also other parts of the body. In 1948 Gruenwald described a case of rheumatoid disease with visceral lesions and commented that this combination had not been reported previously except for

passing mention of nodules in subcutaneous tissues, skeletal muscles and nerve trunks, also scars of rheumatic heart disease. The case cited had granulomatous lesions in the heart, pleura and capsule of the spleen indicating that all serous membranes may be involved.

Baggenstoss, Rosenberg and Hench described thirty cases of rheumatoid disease examined at

autopsy. A high incidence of cardiac lesions in distinguishable from those of rheumatic fever was found also a relative frequency of microscopic renal lesions. Although pneumonia chronic suppurative embolism and massive collapse of the lung were the most common causes of death the authors could find no distinguishing pulmonary lesions which could be correlated with the rheumatoid disease. Nor could they find any relationship between the frequent finding of fibrinous pleural adhesions which were present in twenty-two of the thirty cases.

The Tenth Rheumatism Review published in 1953 contains for the first time three references in which are described five cases of rheumatoid disease with pulmonary lesions. In 1954 Harris was able to collect references to a total of twenty cases of pulmonary lesions associated with rheumatoid disease and cited a case of his own. Five of these cases had been studied at autopsy. Five additional cases are on record by Christie. Two of these cases have been studied at autopsy. Five additional cases are on record of patients examined at autopsy who showed pulmonary lesions. One by Bevan and co workers and the other by Katz and Luerbach. Within the space of two years I have had occasion to study six patients with acute rheumatoid disease with characteristic articular manifestations in whom the pulmonary lesions were in keeping with a systemic disturbance. In three of these it was possible to obtain lung biopsies for histological study. The roentgenological and pathological findings resembled in some respects those seen in rheumatic pneumonia and in several other members of the collagen group of diseases, also in occasional instances of diffuse interstitial fibrosis.

The pathology of the pulmonary lesions in rheumatoid disease has been studied intensively by Christie who describes the histological appearances as follows: (a) proliferation of mononuclear cells in the alveolar septa with occasional sharply localized areas of fibrinous pneumonia constituting a more severe grade of parenchymatous lesions. (c) connective tissue buds resembling those described by Mason and by Neuberger and co workers in rheumatic pneumonia are sometimes present. These consist of minute nodules of connective tissue lying in the alveolar ducts budding from the wall. (d) focal scars of variable density in the pleura alveolar walls bronchial vessels and peribronchovascular connective tissue. Much of the fibrous is nonspecific although such areas usually contain more advanced foci recognizable as rheumatoid nodules. (e) focal scarring or diffuse fibrosis in the walls of the small pulmonary vessels and of the bronchial arteries and (f) acute fibrinous pleurisy and chronic pleural scarring independent of or in association with other pulmonary changes.

A study of the pulmonary lesions occurring in rheumatoid disease brings out a number of clinical and roentgenological features in addition to the pathological changes described which would indicate that the pulmonary lesions like the joint lesions are part of the same disturbance. The histories of five of the six patients personally studied indicated a preexisting hypersensitivity in the form of urticaria of unknown cause or allergic reactions to sulfonamide or penicillin. The case reported by Katz and Luerbach showed sensitivity to iodine. In the case reported by Bloom and J. H. Rubin it was suspected that anaphylactic reaction. Leys and Swift reported that the factor of heredity and allergy explained the rheumatoid disease in their patient. Lillman and Ball claim that the visceral and other lesions of rheumatoid disease may be explained by hypersensitivity manifestations in tissues. The factor of hypersensitivity in rheumatoid disease has been discussed fully in a number of publications by Rich and Gregory and need not be reviewed here. The significance of the occasional finding of L.E. cells in patients with rheumatoid arthritis and other features indicating that rheumatoid disease is apparently one facet of a more widespread systemic disturbance are discussed in various sections of this and later sections.

Of particular significance is the time relationship between the appearance of symptoms and signs of rheumatoid disease and the pulmonary manifestations. In some the latter appear at the time of recrudescence of joint symptoms. In others the joint and pulmonary manifestations



Figure 24 Case 15 Rheumatic pneumonia in a girl A (Left) Heart enlarged with flattening of left border lungs clear B (Right) Two weeks later fan shaped fluffy densities radiating into the central zones of both lungs marked increase in size of heart (Autopsy showed rheumatic endocarditis of mitral and tricuspid valves congestion and edema of lungs with thickening of septa and mononuclear cell permeation rheumatic pneumonia duration of illness seven months)

small amount of clear yellowish tinged fluid was present in each pleural cavity. The lungs were firm but crepitant and floated in water. They were patchy dark and light red with grayish mottling and slightly edematous. The bronchi and pulmonary vessels were normal. The peribronchial nodes were soft and slightly enlarged. The heart was markedly hypertrophied and all chambers were dilated. The mitral ring was dilated edges of cusps were thickened and verrucous at the coaptation of the border. Tricuspid was dilated with verrucae at the border. The left ventricle measures 15 mm in thickness the right ventricle 9 mm.

Microscopic examination revealed in the lungs the septa thickened by edema and numerous red

blood cells. The alveoli in scattered areas contained many mononuclear cells some of the larger cells containing brown pigment. There was marked congestion. Within many of the alveoli edema was present. The heart revealed scattered areas of fibrinous collagen degeneration in the myocardium in which Aschoff cells mononuclears and some polymorphonuclear cells were found. At the coaptation border of the mitral and tricuspid valves hyalinized nodules and verrucae were clearly seen. The diagnosis was rheumatic heart disease enlarged heart mitral insufficiency and tricuspid insufficiency, endocarditis, cerebral edema ascites hydrothorax chronic passive congestion of liver and lung and rheumatic pneumonia.

Pulmonary Lesions in "Rheumatoid Disease"

Rheumatoid disease,' according to Ellman, is a more descriptive term than rheumatoid arthritis because the former expresses a widespread process affecting not only the locomotor but also other parts of the body. In 1948, Gruenwald described a case of rheumatoid disease with visceral lesions and commented that this combination had not been reported previously except for

passing mention of nodules in subcutaneous tissues skeletal muscles and nerve trunks also scars of rheumatic heart disease. The case cited had granulomatous lesions in the heart, pleura and capsule of the spleen indicating that all serous membranes may be involved.

Baggenstoss, Rosenberg and Hench described thirty cases of rheumatoid disease examined at

autopsy. A high incidence of cardiac lesions, indistinguishable from those of rheumatic fever was found, also a relative frequency of microscopic renal lesions. Although pneumonia, chronic sup-
puration, embolism and massive collapse of the lung were the most common causes of death, the authors could find no distinguishing pulmonary lesions which could be correlated with the rheumatoid disease. Nor could they find any relationship between the frequent finding of fibrous pleural adhesions which were present in twenty of the thirty cases.

The Tenth Rheumatism Review, published in 1953, confirms, for the first time three references in which are described five cases of rheumatoid disease with pulmonary lesions. In 1954, Harris was able to collect references to a total of twenty cases of pulmonary lesions associated with rheumatoid disease and cited a case of his own. Five of these cases had been studied at autopsy, two by Ellman and Ball and three by Christie. Two additional cases are on record of patients examined at autopsy who showed pulmonary lesions, one by Bevan and co workers and the other by Katz and Auerbach. Within the space of two years, I have had occasion to study six patients with acute rheumatoid disease with characteristic articular manifestations in whom the pulmonary lesions were in keeping with a systemic disturbance. In three of these it was possible to obtain lung biopsies for histologic study. The roentgenological and pathological findings resembled in some respects those seen in rheumatic pneumonia and in several other members of the collagen group of diseases, also on occasional instances of diffuse interstitial fibrosis.

The pathology of the pulmonary lesions in rheumatoid disease has been studied intensively by Christie who describes the histological appearances as follows: (a) proliferation of mononuclear cells in the alveolar septa with occasional sharply localized areas of fibrous pneumonia constituting a more severe grade of pneumonitis, (c) connective tissue buds resembling those described by Mason and by Neuberger and co workers in rheumatic pneumonia are sometimes present. These consist of

minute nodules of connective tissue lying in alveolar ducts, budding from the wall, (d) focal scars of variable density in the pleura, alveolar walls, bronchi, vessels and peribronchial and perivascular connective tissue. Much of the fibrosis is nonspecific although such areas usually contain more advanced foci recognizable as 'rheumatoid nodules, (e) focal scarring or diffuse fibrosis in the walls of the small pulmonary vessels and of the bronchial arteries, and (f) acute fibrous pleurisy and chronic pleural scarring independently of or in association with other pulmonary changes.

A study of the pulmonary lesions occurring in rheumatoid disease brings out a number of clinical and roentgenological features, in addition to the pathological changes described, which would indicate that the pulmonary lesions, like the joint lesions, are part of the same disturbance. The histories of five of the six patients, personally studied, indicated a preexisting hypersensitivity in the form of urticaria of unknown cause or allergic reactions to sulfonamide or penicillin. The case reported by Katz and Auerbach showed sensitivity to iodine. In the case reported by Bloom and J H Rubin, it was suspected that anaphylactic reaction. Lewis and Swift reported that the factor of heredity and allergy explained the rheumatoid disease in their patient. Ellman and Ball claim that the visceral and other lesions of rheumatoid disease may be explained by hypersensitivity manifestations in tissues. The factor of hypersensitivity in rheumatoid disease has been discussed fully in a number of publications by Rich and Gregory, and need not be reviewed here. The significance of the occasional finding of LE cells in patients with rheumatoid arthritis and other features indicating that 'rheumatoid disease' is apparently one facet of a more widespread systemic disturbance, are discussed in various sections of this and later sections.

Of particular significance is the time relationship between the appearance of symptoms and signs of rheumatoid disease and the pulmonary manifestations. In some, the latter appear at the time of recrudescence of joint symptoms. In others, the joint and pulmonary manifestations



Figure 24 Case 15 Rt. — — — — —
lungs clear B (Right)

lungs, marked increase
congestion and edema of lungs with thickening of septa and mononuclear cell permeation, rheumatic pneumonia, duration of illness seven months)

border,
of both
valves

small amount of clear, yellowish tinged fluid was present in each pleural cavity. The lungs were firm but crepitant and floated in water. They were patchy, dark and light red with grayish mottling and slightly edematous. The bronchi and pulmonary vessels were normal. The peribronchial nodes were soft and slightly enlarged. The heart was markedly hypertrophied and all chambers were dilated. The mitral ring was dilated, edges of cusps were thickened and verrucous at the coaptation of the border. Tricuspid was dilated with verrucae at the border. The left ventricle measures 15 mm in thickness, the right ventricle 9 mm.

Microscopic examination revealed in the lungs the septa thickened by edema and numerous red

blood cells. The alveoli in scattered areas contained many mononuclear cells, some of the larger cells containing brown pigment. There was marked congestion. Within many of the alveoli edema was present. The heart revealed scattered areas of fibrinous collagen degeneration in the myocardium in which Aschoff cells, mononuclears and some polymorphonuclear cells were found. At the coaptation border of the mitral and tricuspid valves hyalinized nodules and verrucae were clearly seen. The diagnosis was rheumatic heart disease, enlarged heart, mitral insufficiency and tricuspid insufficiency, endocarditis, cerebral edema, ascites, hydrothorax, chronic passive congestion of liver and lung and rheumatic pneumonia.

Pulmonary Lesions in "Rheumatoid Disease"

"Rheumatoid disease," according to Ellman, is a more descriptive term than rheumatoid arthritis because the former expresses a widespread process affecting not only the locomotor but also other parts of the body. In 1948, Gruenwald described a case of rheumatoid disease with visceral lesions and commented that this combination had not been reported previously except for

passing mention of nodules in subcutaneous tissues, skeletal muscles and nerve trunks, also scars of rheumatic heart disease. The case cited had granulomatous lesions in the heart, pleura and capsule of the spleen indicating that all serous membranes may be involved.

Baggenstoss, Rosenberg and Hench described thirty cases of rheumatoid disease examined at

autopsy. A high incidence of cardiac lesions, indistinguishable from those of rheumatic fever, was found also a relative frequency of microscopic renal lesions. Although pneumonia, chronic suppurative, embolism and massive collapse of the lung were the most common causes of death the authors could find no distinguishing pulmonary lesions which could be correlated with the rheumatoid disease. Nor could they find any relationship between the frequent finding of fibrous pleural adhesions which were present in twenty-two of the thirty cases.

The Tenth Rheumatism Review published in 1953, contains, for the first time three references in which are described five cases of rheumatoid disease with pulmonary lesions. In 1954, Harris was able to collect references to a total of twenty cases of pulmonary lesions associated with rheumatoid disease and cited a case of his own. Five of these cases had been studied at autopsy. Five by Ellman and Ball and three by Christie. Two additional cases are on record of patients examined at autopsy who showed pulmonary lesions, one by Bevan and co-workers and the other by Katz and Auerbach. Within the space of two years, I have had occasion to study six patients with acute rheumatoid disease with characteristic articular manifestations in whom the pulmonary lesions were in keeping with a systemic disturbance. In three of these, it was possible to obtain lung biopsies for histologic study. The roentgenological and pathological findings resembled in some respects those seen in rheumatic pneumonia and in several other members of the collagen group of diseases also in occasional instances of diffuse interstitial fibrosis.

The pathology of the pulmonary lesions in rheumatoid disease has been studied intensively by Christie who describes the histological appearances as follows: (a) proliferation of mononuclear cells in the alveolar septa with occasional sharply localized areas of fibrous pneumonia constituting a more severe grade of parenchymatous lesions (c) connective tissue "buds" resembling those described by Masson and by Neuberger and co-workers in rheumatic pneumonia are sometimes present. These consist of

minute nodules of connective tissue lying in alveolar ducts, budding from the wall, (d) focal scars of variable density in the wall, alveolar walls, bronchi, vessels and peribronchial and perivascular connective tissue. Much of the fibrosis is nonspecific although such areas usually contain more advanced foci recognizable as "rheumatoid nodules," (e) focal scarring or diffuse fibrosis in the walls of the small pulmonary vessels and of the bronchial arteries, and (f) acute fibrous pleurisy and chronic pleural scarring independently of or in association with other pulmonary changes.

A study of the pulmonary lesions occurring in rheumatoid disease brings out a number of clinical and roentgenological features, in addition to the pathological changes described, which would indicate that the pulmonary lesions, like the joint lesions, are part of the same disturbance. The histories of five of the six patients, personally studied, indicated a preexisting hypersensitivity in the form of urticaria of unknown cause or allergic reactions to sulfonamide or penicillin. The case reported by Katz and Auerbach showed sensitivity to iodine. In the case reported by Bloom and J. H. Rubin, it was suspected that anaphylactic reaction. Levis and Swift reported that the factor of heredity and allergy explained the rheumatoid disease in their patient. Ellman and Ball claim that the visceral and other lesions of rheumatoid disease may be explained by hypersensitivity manifestations in tissues. The factor of hypersensitivity in rheumatoid disease has been discussed fully in a number of publications by Rich and Gregory and need not be reviewed here. The significance of the occasional finding of L.E. cells in patients with rheumatoid arthritis and other features indicating that "rheumatoid disease" is apparently one facet of a more widespread systemic disturbance, are discussed in various sections of this and later sections.

Of particular significance is the time relationship between the appearance of symptoms and manifestations of rheumatoid disease and the pulmonary manifestations. In some, the latter appear at the time of recrudescence of joint symptoms. In others, the joint and pulmonary manifestations

appear at the same time. In still others, a non-descript "pneumonia" or "pleurisy" precedes for a brief period the joint symptoms and with the appearance of swollen, painful joints, the pulmonary disease appears to become activated. The later course of events is characterized by a degree of parallelism in the symptoms referable to both joint and lung lesions.

The chest x-ray findings in rheumatoid disease are of major interest since the lung changes portray the dynamic phases in the evolution of the process. At times, the pulmonary infiltrations are transitory. The most frequent expression of rheumatoid disease in the chest is in a pleurisy, the latter manifesting itself in small serous effusions, large collections of fluid are more apt to be associated with cardiac failure. The frequent elicitation of a friction rub on auscultation and the almost inevitable presence of fibrinous or a dense pleural reaction in biopsy or autopsy specimens bears emphasis.

The chest x-rays usually show bilateral, more-or-less, symmetrical infiltrations. One of the cases described by Christie showed roentgenologically a round, dense shadow 6 cm in diameter in right upper lobe. Autopsy revealed it to be a large granuloma with histological features similar to those found in the periarthritic nodules of rheumatoid disease. The infiltrations may be small and evenly distributed simulating miliary tuberculosis or they may be of a nodular character affecting chiefly the mid and lower lung fields simulating sarcoidosis, inhalational dust diseases or bronchogenic tuberculosis. The infiltrations may be irregular and of patchy distribution in keeping with a viral or bacterial bronchopneumonia. After the subsidence of the acute stage of the disease, the markings assume a more linear configuration of a delicate or coarse reticular network, such as one sees in lymphangitic carcinomatosis or diffuse interstitial fibrosis of the lungs. In long standing disease, secondary bronchopneumonia and suppuration tend to obscure the basic pattern.

Caplan described a syndrome in coal workers in which rheumatoid arthritis is associated with nodular fibrosis of the lung roentgenologically similar to, but distinguishable from, the pro-

gressive massive fibrosis of coal miner's pneumoconiosis. According to Miall, Caplan and co-workers, the pulmonary lesions have no similarity to the interstitial pneumonitis occurring in cases of rheumatoid arthritis, described by Ellman and Ball and referred to previously. The "rheumatoid" lung lesions, described by Caplan, develop fairly rapidly and appear as numerous discrete, rounded opacities scattered diffusely throughout both lung fields. The lesions seem to appear in crops, change in size relatively little but may enlarge and undergo cavitation. An epidemiological study revealed that whereas rheumatoid arthritis occurs in over 50 per cent of coal-miners with the characteristic lesions, rheumatoid arthritis occurs in only 3 per cent of coal miners with conventional forms of progressive massive fibrosis. The exact nature of Caplan's syndrome is still to be determined.

There is no characteristic picture typifying the pulmonary lesions in rheumatoid disease. But if one views the chest x-ray appearance in the light of the history, physical examination and laboratory findings, one may discern in the film "roentgenological equivalents" which may be present in kindred conditions in the same sense that the histological findings offer "morphological equivalents."

Case 16 Female—Age 46

A Negro female became ill on December 20, 1953 with fever, cough, dyspnea and painful swollen joints. The patient was bed ridden at home for two weeks and treated with penicillin. Although not fully recovered, she returned to work as a domestic. On February 20, 1954 there was a return of fever, cough, painful joints and at this time the patient also had chest pain and, on one occasion spat up a small amount of blood. The patient was hospitalized on March 11, 1954. Examination revealed an acutely ill dyspneic woman, temperature 103° F, pulse 110, respiration rate 24, blood pressure 100/80. Both hands, especially the left, showed fusiform tender swellings of the interphalangeal joints. The right knee was also swollen and tender. Examination of the chest revealed dullness over both sides and ribs at the bases. The heart revealed no abnormal findings. The diagnosis was bilateral bronchopneumonia and rheumatoid arthritis, or,

possibly acute rheumatic fever and rheumatic pneumonia.

Chest x rays revealed irregular patchy infiltrations throughout both lungs chiefly the left in keeping with an acute bronchopneumonia; there was a pleural reaction at the bases (Figure 25A). The heart was not enlarged. X rays of the hands showed fusiform swelling of the interphalangeal joints. The joints themselves were not involved. Laboratory tests revealed an accelerated erythrocyte sedimentation rate, hemoglobin 79 per cent, red blood cells 4,220,000 per cu mm, white blood cells 8,700 per cu mm with a normal differential. Urine was negative. Mazzini was negative. On a later occasion Mazzini + Wassermann 4+. Serum albumin 3.2 mg per cent, serum globulin 3.2 mg per cent, on a later occasion the albumin was 2.6 mg per cent and the globulin 3.5 mg per cent. Electrocardiogram showed no abnormalities. The patient was treated with combined antibiotics later with penicillin alone, also salicylates and sedatives. After one month penicillin treatment the patient developed a generalized rash which gradually subsided. It was ascribed to penicillin sensitivity. Although the chest x rays after three weeks showed considerable clearing of the lung fields the rales persisted. The joint pains slowly abated, the fever declined and the patient was discharged on April 24, 1954.

Six days later the patient was admitted to the Morrisania City Hospital because of recurrence of fever, cough, chest and joint pains. The patient was acutely ill and dyspneic. The rash was still present over the chest and upper arms. The fingers, toes and knees were swollen and painful on motion. No abnormalities were found in the heart. On auscultation numerous rales were heard in both lungs with a pleural friction rub at the right base. Extensive laboratory studies were noninformative. Chest x rays now revealed fine diffuse interstitial striations throughout both lungs, especially the right and less of the pneumonic exudate seen in previous films, pleural reaction at bases (Figures 25 B and C). The patient continued to have low grade fever. Under salicylates the joint pains gradually subsided and the patient was discharged on May 26, 1954.

The patient was readmitted to the Morrisania City Hospital on July 1, 1954 because of recurrence of pain in the hands, wrists, shoulders and ankles and swelling of the affected parts. The patient was dyspneic and complained of a feeling of chest oppression. Physical x ray and laboratory examina-

tions revealed few changes from those noted previously. On July 2, 1954 a biopsy of the right lower lobe was done by Dr. M. Rubin. The excised specimen was examined by Dr. R. Lubliner. The lung was found somewhat firmer than normal but fairly well aerated; the pleura slightly thickened. Cut section revealed pinkish red parenchyma through which were scattered small strands of despressed grayish tissue. Microscopic examination showed marked alteration of normal architecture, foci of well aerated parenchyma alternating with foci of atelectasis. There was thickening of interalveolar septa due to increased vascularity, cellular infiltration and patchy fibrosis. In many instances there was hyaline thickening of the walls of the small vessels within the septa. The cellular infiltration was mononuclear with a large number of plasma cells. There was marked hyperplasia of the alveolar lining cells. There was slight fibrous thickening of the pleura and of the interlobular septa. There was moderate thickening of the interalveolar septa also in well aerated areas. The diagnosis was interstitial and organizing pneumonia with patch pulmonary fibrosis (Figure 25D).

The patient was treated with salicylates and sedation. The joint pains gradually subsided. She still had a low grade fever at the time of her discharge on July 23, 1954. A chest x ray revealed a slight decrease in the pulmonary markings. The pleural reaction was still present at both costophrenic sinuses. In November 1954 the patient had a recurrence of painful swollen knees and ankles and she was admitted to the Bronx Municipal Hospital Center where she remained until May 23, 1955.

Laboratory examinations including repeated L.E. tests were unrevealing. The patient was treated with various measures including butazolidin, antibiotics, salicylates and for about six weeks with cortisone. There was a moderate degree of improvement in her rheumatoid symptoms. The chest x rays also showed a temporary decrease in the degree of interstitial markings but not to a striking degree. She is presently under observation in the clinic. A chest x ray taken in November 1955 showed a considerable increase in the interstitial striations throughout both lungs. The symptoms remained the same.

Before concluding the discussion of the pulmonary lesions of rheumatoid disease it might be mentioned that the lesions are not unlike those encountered in rheumatic pneumonia described

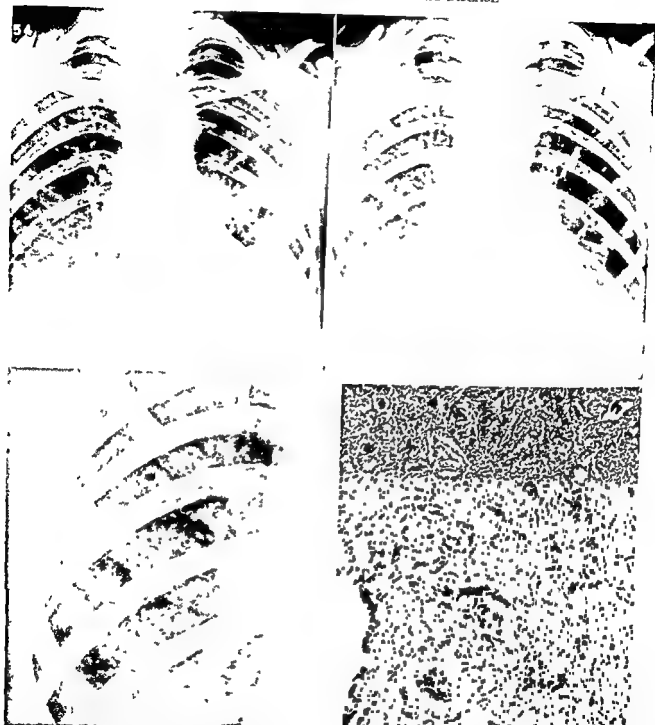


Figure 25 Case 16 Rheumatoid disease with pulmonary lesions A (Upper left) Irregular, patchy infiltrations in both lungs, chiefly the left lower B (Upper right) Two months later, diffuse reticulations in both lungs, pleural reaction at bases C (Lower left) Lung detail showing fine striations D (Lower right)

Lung (Biopsy) specimen shows diffuse interstitial fibrosis, interalveolar septal thickening, hyaline thickening of walls of small blood vessels, exudate in alveoli (From Rubin *Am J Med*, 1959, 1975)

ALLERGIC DISEASES (CONCLUDED)

in the preceding section. It is also well known that the lung changes in rheumatic pneumonia and virus pneumonia have many features in common including the presence of a hyaline membrane mononuclear cell infiltration nonbacterial edema. In fact rheumatic pneumonia may be mistaken for a virus infection and some believe that at least a small proportion of the latter are instances of rheumatic pneumonia. Hurthead and Haley reported the case of a twenty five year old white woman who presented the concomitant occurrence of known healed inactive cardiac lesions and a peculiar interstitial pneumonitis. The pneumonitis was widespread demonstrating a healed proliferative phase with extensive fibrosis and an active exudative phase. In addition partly healed arterial lesions were observed in the lungs. The authors point out that this case offered an additional point of interest in that the pulmonary lesions resembled in certain respects the changes described by Hamman and Rich in their cases of interstitial pulmonary fibrosis. This brings up a rather intriguing subject which merits special consideration.

The reason for including the Hamman Rich syndrome in the section on allergic diseases is because there is evidence that in some cases at least the condition is associated with hypersensitivity. Furthermore the Hamman Rich syndrome enters into the differential diagnosis of many cases in which the chest x ray reveals diffuse interstitial pulmonary infiltrations. For the present the discussion will limit itself to those forms of the Hamman Rich syndrome in which there is reason to believe that hypersensitivity plays an important role.

Diffuse Interstitial Fibrosis of the Lungs Hamman Rich Syndrome

Since the introduction of the sulfonamides penicillin streptomycin and other specific antimicrobial agents the picture of the bacterial pneumonias has changed remarkably. Not only has there been a precipitous decline in the incidence of lobar pneumonia but even the atypical forms are often bizarre. One of these is a pneumonia characterized by diffuse interstitial fibrosis of the lungs. This unusual disease was first brought to medical attention by Hamman and Rich in 1944 as an acutely progressive and fatal pneumonia. But it soon became apparent that diffuse interstitial fibrosis of the lungs may be slowly progressive over a period of years. There is reason to suspect however that many patients recover. The frequency with which the disease takes place cannot be gauged accurately because the diagnosis rests on certain changes in the lungs which are demonstrable only at autopsy or by lung biopsy.

A recent report by Wildberger and Barclay refers to thirty reported cases of the Hamman Rich syndrome. This number gives an erroneous impression of the true incidence of the disease as it is currently being encountered. This is borne out by the fact that of 7 collected series of 197

cases reported from only three sources in which lung biopsies were done for obscure pulmonary disease no less than sixty one showed interstitial or idiopathic pneumonitis with or without fibrosis and/or emphysema (see Table II). Undoubtedly a considerable number of these represented instances of the Hamman Rich syndrome. Dr Lubliner and I are presently studying a group of eighteen cases of the disease all proved by lung biopsy or autopsy or both observed at the Montefiore Hospital.

PATHOGENESIS

The widespread use of antimicrobial agents may be one of the causes for the increasing incidence of atypical pneumonias of the type in which we are concerned at the moment. Auerbach and co workers point out that solution of fibrin has long been held to be a function of enzymes derived from polymorphonuclear leukocytes. Exudates which are rich in fibrin and These investigators suggest that the widespread use of potent antimicrobial agents is contributing to a rising incidence of premature organization of pulmonary exudates with resulting fibrosis of lung tissue. In this respect it should be noted

that an analogous situation is currently being encountered in pulmonary tuberculosis

Golden and Tullis also express the view that interstitial fibrosis may be on the basis of failure of resolution and subsequent organization following one or more attacks of acute interstitial pneumonitis ("primary atypical pneumonia") Geever and co-workers have shown that alveolar cells accumulate under various pathologic conditions, especially in pneumonias associated with virus infections, in which case the irritant factor is capable of producing septal cell proliferation and actual lining. The tendency to proliferation is marked among the cells along the interlobular septa and, to a lesser degree, in perivascular and peribronchial areas. These investigators draw attention to the fact that the inert lining may interfere with respiratory function. Ogilvie and Hulse also suspect that the interstitial fibrosis is derived from the organization of the hyaline membrane which lines the alveoli during the acute stages of the disease.

In their original communication, Hamman and Rich note that Winternitz had examined the specimens obtained from their patients with acute diffuse interstitial fibrosis of the lungs and found a striking resemblance to that found in the lungs of animals during experimental investigations on influenzal pneumonia. The lung biopsy specimens of three patients with diffuse interstitial fibrosis associated with rheumatoid disease, referred to in the previous section as well as material of a larger group of patients with diffuse interstitial pulmonary fibrosis which Dr. Ruth Lubliner and I have been studying for the past several years, were reviewed on various occasions by Zimmerman. He also noted in the histology of many of the specimens features closely resembling those found in viral bronchopneumonia.

An additional cause, or possibly an accessory factor, in the development of diffuse interstitial fibrosis of the lungs may lie in the allergic reactions which often accompany sulfonamide and penicillin treatment of atypical pneumonias. Hamman and Rich drew attention in their publication to a group of cases of "Current Bronchopneumonia of Unusual Character and Undetermined Etiology," which had been reported previ-

ously by Kneeland and Smetana, in which one of the cases corresponded clinically and anatomically with theirs. In the particular instance, a woman of forty-seven developed urticaria simultaneously with chills and blood streaked sputum. The patient was found to have progressive bronchopneumonia and was soon complicated by thrombophlebitis, anemia, hypoproteinemia and right-sided heart failure leading to death. At autopsy lesions were found in the pulmonary arteries suggestive of polyarteritis nodosa, in addition to diffuse interstitial pulmonary lesions characterized by a mononuclear cell exudate and a tendency to organization also thickening of alveolar septa and narrowing of alveolar spaces. The patient had received sulfa pyridine and the vascular changes may have been related to the drug.

Among the fifty-two patients with atypical bronchopneumonia, described by Kneeland and Smetana, was a group of six "in whom the clinical picture of a severe and prolonged bronchopneumonia was complicated by a variety of phenomena suggesting that tissues other than pulmonary alone were involved. Among these phenomena were migratory polyarthritides, erythematous skin eruptions, slight enlargement of the spleen and lymph glands, jaundice, gross hematuria, fibrinous pericarditis and encephalitis. All six happened to be females and as these perplexing clinical panoramas unfolded themselves the notion kept recurring that there must be an associated element of diffuse vascular disease of the type seen in disseminated lupus or periarthritis nodosa."

It is difficult to determine to what degree the element of hypersensitivity plays a role in the Hamman Rich syndrome. It is noteworthy, however, that there is a close similarity in the histological appearances of the pulmonary lesions found in this disease and in those encountered in rheumatic pneumonia, "rheumatoid disease" and the other collagen diseases. Of particular significance is the fact that pulmonary lesions, apparently identical with those observed in acute interstitial pulmonary fibrosis, have been recently observed in patients with hypertension who are under prolonged treatment with hexamethonium

and hydralazine compounds. The interstitial pneumonitis may progress quite rapidly in some cases. Noteworthy, too, is the fact that the so-called hydralazine syndrome is associated with fever, rheumatoid symptoms and in its severer forms with signs of acute disseminated lupus erythematosus including the occasional finding of L.E. cells. Additional comments on this phenomenon a man-made disease will be found in Chapter 12.

As mentioned briefly in the section dealing with the pulmonary lesions in rheumatoid disease it appears that for one reason or another in some patients with systemic diseases of the types described in these pages the respiratory tract sustains the brunt of the damage while other organs are only slightly affected or even escape injury at least insofar as the latter can be recognized clinically. This feature is forcefully brought to one's attention when a patient with a systemic disease including pulmonary lesions dies and the organs are examined at autopsy. Excepting the lungs the other organs may show surprisingly little in the way of demonstrable tissue changes to indicate that the body had once been the seat of a widespread and profound disturbance. Yet the clinical course of the disease may have been punctuated by a series of dramatic events affecting various parts of the body. In this respect the clinician is occasionally in a more favorable position to evaluate the post-mortem findings than the pathologist who not appreciating fully what had transpired during the patient's lifetime may find only fibrosis in the lungs an end stage of all manner of healed or partially healed disease. With increasing use of lung biopsies performed relatively early in the course of systemic diseases which are accompanied by pulmonary lesions one is occasionally able to detect features in the lungs which indicate that the pulmonary involvement is part of a generalized disturbance although the exact nature of the latter is not always ascertainable.

CLINICAL FEATURES

Kahn, Peeler and I described a typical case of diffuse interstitial fibrosis of the lungs and reviewed twelve cases reported to date (1957).

Since then the literature on the subject has grown considerably. Suffice it to state that the elements which influence the variability in the clinical picture may be related in part to the underlying cause, in part to the severity of the disease, in part to hypersensitivity of certain tissues to specific agents, in part possibly also to the antimicrobial treatment and to factors still unknown. If the fibrosis of the lungs is acutely progressive death may result from anoxia due to alveolar capillary block, the thickened alveolar membrane preventing diffusion of gases (Austrian and co-workers). If the disease evolves slowly over a number of years there is increasing obstruction of blood flow and hypertension of the lesser circulation leading to chronic cor pulmonale. Clubbing of the fingers at times of a striking degree is often encountered. In still others the lungs undergo diffuse hardening with focal emphysema and bronchiolectasis in a cystic lung similar to a type of cirrhotic organ encountered after the 1918 pandemic of influenza and now seen sporadically.

It is impossible to judge how often diffuse interstitial disease of the lungs resolves without causing irreversible damage of the organs. But this outcome probably occurs more often than is realized since the disease usually masks itself as an atypical or viral pneumonia. The fact that the treatment with ACTH or cortisone of acutely progressive disease may be followed by dramatic improvement indicates that the disease may be reversible at certain stages in spite of the fact that roentgenologically the process appears to be well organized. A word of caution is in order regarding the use of ACTH or cortisone in the treatment of the disease. Perbody and co-workers also Schechter and others warn against the sudden withdrawal of the steroids once begun lest an acute and possibly fatal rebound reaction occurs. Once initiated steroid treatment has to be continued indefinitely and discontinued very slowly if one is forced to do so.

With respect to the possible role which hypersensitivity may play in causing diffuse interstitial fibrosis of the lungs the case histories of the following two sisters are most instructive. A somewhat analogous experience was documented



Figure 26 Case 17 Interstitial pulmonary fibrosis of probably allergic etiology, in sisters A (Left) Diffuse reticular markings in both lungs more marked in upper lobes B (Right) Three years later marked increase in interstitial infiltrations with minute areas of honeycombing in upper lobes (Death one year later caused by respiratory failure Autopsy disclosed scattered small air cysts interstitial fibrosis diffuse emphysema and bronchopneumonia See Case 18)

by Peabody and co workers in the case of identical twin sisters At the time of the report by these authors the findings had been confirmed at autopsy in one of the sisters Later MacMillan reported that the surviving sister had also died and had revealed at autopsy lung findings identical with those of the twin MacMillan's communication dealt with familial pulmonary fibrosis Wildberger and Barclay also reported the finding of diffuse interstitial pulmonary fibrosis in siblings in whom the disease had been evolving over a period of approximately ten years The occurrence of a comparatively infrequent disease in members of the same family speaks for a genetic factor In the following case reports of two sisters hypersensitivity may have played a role

Case 17 Female—Age 40

The patient's illness began in 1946 with cough productive of mucoid and bloody sputum also exertional dyspnea orthopnea and weight loss A chest x ray taken at a Board of Health Clinic revealed minimal fibrosis in both lungs By the end

of 1948 the pulmonary infiltrations became much more noticeable The sputum being negative for tubercle bacilli a provisional diagnosis of sarcoidosis was made Of interest in the patient's past and family histories was the fact that she had a severe form of dermatitis which took many years to clear up The patient's sister whose case history will be cited shortly had hay fever and was allergic to drugs especially aspirin which caused the skin to swell and itch Several other members of the family had hay fever

In the Spring of 1949 the patient was admitted to the Department of Internal Medicine of the University Hospital Michigan and the following notes of the case record were kindly supplied The patient was a thin pale white female who appeared to be chronically ill The only positive findings on physical examination were the presence of clubbed fingers and toes and rales at the lung bases Various laboratory tests were done but the findings were within normal limits The chest x ray showed widespread granular coalescing lesions in both lungs Bronchoscopic examination showed a normal tracheobronchial tree Sarcoidosis was suspected At the time of the patient's last examination

at the University Hospital she was quite upset, complaining of cough, insomnia and dyspnea.

I examined the patient for the first time on September 30, 1949. The patient weighed 70 lbs. She had excessive cough, expectoration and dyspnea. Chest x-rays revealed diffuse interstitial fibrosis of both lungs with innumerable cystic spaces throughout both organs (Figure 26). Because of increasing symptoms the patient was admitted to Fordham Hospital where she required constant oxygen administration because of her respiratory distress. The patient's condition steadily worsened and she died on July 13, 1950, approximately four years from the time of onset of symptoms.

At autopsy the major findings were limited to the thoracic organs. The heart weighed 320 grams. There was mild calcification of the tricuspid and mitral valves. There was no evidence of arterio-sclerotic changes in the coronary vessels or aorta. No adherent thrombi were found in the heart chambers. The surfaces of both lungs were covered by emphysematous blebs about the size of marbles. The blebs contained no fluid or exudate. The lower lobes were dark purple in color and of a liver-like consistency. On cut section the lungs revealed a most inelastic tissue with small air cysts

scattered throughout the parenchyma. Microscopic examination showed extensive pulmonary fibrosis causing destruction of lung parenchyma. There were large, irregular patches of fibrosis with a few scattered entrapped alveolar spaces, distended and lined by hyperplastic cuboidal cells. Adjacent to scars were patches of emphysema alternating with patches of atelectasis. The latter showed fibrous thickening of interalveolar septa, no inflammatory cell infiltration. There was moderate thickening of vessel walls secondary to the fibrosis. The anatomical diagnosis was diffuse chronic cystic disease and interstitial fibrosis, diffuse emphysema, bronchopneumonia.

Case 18 Female—Age 58

The patient became ill late in 1948 with cough, expectoration and dyspnea. Except for the presence of rales at the lung bases the physical examination by her physician revealed no significant abnormalities. A chest x-ray showed diffuse fibrosis of both lungs. A Mantoux test was negative. The sputum was negative for acid fast organisms. The patient's symptoms slowly increased. At this time a bronchoscopy was done and no abnormalities were found. No glands presented themselves



Figure 27 Case 18 Interstitial pulmonary fibrosis of probably allergic origin in sisters. A (Left) Diffuse reticulations throughout both lungs. B (Right) Lung. Diffuse fibrosis and honeycombing. (Histologic examination showed marked thickening of interalveolar septa, increased vascularity, and mononuclear cell infiltration, hyperplasia of alveolar lining cells, patches of interstitial fibrosis and foci of recent bronchopneumonia. (See Case 17.)

for biopsy. It was the impression of the attending physician that the patient had sarcoidosis or a non-specific pulmonary fibrosis of undetermined etiology. A chest x ray taken in August, 1950 revealed no significant changes from those noted a year previously (Figure 27A).

Of additional interest in the patient's history was the fact that she had a salpingectomy and oophorectomy and had received radiotherapy five years previously. The patient stated that for many years she had been having hay fever and as a young woman had suffered of an allergic dermatitis. The patient's sister whose history was cited previously also suffered of allergies as did several other members of the family. The patient managed to be up and about until the middle of 1951 when she was forced to spend increasingly more time in a chair and later in bed because of dyspnea and recurring febrile episodes.

I examined the patient for the first time on September 15, 1951 when she was admitted to a hospital in acute respiratory distress which was only partially relieved by oxygen. Examination revealed a gray haired small shriveled woman of about 70 or 80 lbs in weight who appeared considerably older than her stated age. The percussion note was resonant over both sides of the chest except in the left axilla. On auscultation very few rales were heard on the right side but rhonchi were heard in the left and moist rales at both bases. The heart rate was rapid, no murmurs were heard. The abdomen was flaccid, the liver was palpable but did not seem enlarged. There was no edema of the extremities. A bedside chest x ray taken the day previously revealed mottled infiltrations throughout both lungs and a conglomerate mass of consolidation apparently a pneumonia at the left base. The patient's course was rapidly downhill and she

died the same night. The postmortem examination done under difficulties was limited to the lungs, heart, a piece of liver, spleen and the left kidney.

The lungs revealed nodularity of the pleural surface. On section there was diffuse honeycombing of the organs (Figure 27B). Histological examination showed all variations from early to advanced pulmonary fibrosis and foci of recent bronchopneumonia and purulent bronchitis. Sections revealed alternating foci of emphysema and atelectasis, slight thickening of walls of medium sized blood vessels. Other sections revealed marked thickening of interalveolar septa, increased vascularity and mononuclear cell infiltration, alveolar spaces distorted, elongated, often distended also hyperplasia of alveolar lining cells. Still other sections revealed large patches of interstitial fibrosis in places still fairly cellular, the remaining alveoli spaces distended filled with edema fluid and alveolar macrophages, also foci of bronchopneumonia or organizing pneumonia and interstitial pneumonitis.

In conclusion it may be stated that diffuse interstitial fibrosis of the lungs is probably the end result of a variety of agents. In most instances the cause cannot be determined. Occasionally it is possible to pin a label on the disease if, for example, it occurs in association with sarcoidosis, berilliosis or some other granulomatous condition, or is due to a recognizable viral or bacterial pneumonia. There is also a group where there is reason to suspect that the lesions in the lungs represent the pulmonary manifestations of a hyperergic state, the term used in its broadest sense to include rheumatic pneumonia, rheumatoid arthritis, scleroderma, disseminated lupus erythematosus, and possibly other conditions.

Bibliography

'COLLAGEN DISEASES POLYARTERITIS NODOSA

- BANDWITCH, M. M., POLAKES, S. H., and CHAIKIN, R. Periarthritis Nodosa. Report of Five Cases. *Ann Int Med* 16:1149, 1947.
- BANK, N. The Relationship of Malignant Hypertension to Periarthritis Nodosa in Humans. *J Mt Sinai Hosp* 22:290, 1955.
- BARDEN, R. P., and COOPER, D. A. The Roentgen Appearance of the Chest in Diseases Affecting the Peripheral Vascular System of the Lungs. *Radiology* 51:44, 1948.
- BERGSTRAND, H. Morphological Equivalents in Polyarthritidis Rheumatica Periarthritis Nodosa. *Trans Ent Eosino-*
- phlic Infiltration of the Lung and Other Allergic Syndromes. *J Path & Bact* 58:399, 1946.
- BLANKENHORN, M. A. and KNOWLES, H. C. Periarthritis Nodosa. Recognition and Clinical Symptoms. *Ann Int Med* 41:887, 1954.
- BOYD, L. J. Pulmonary Manifestations of Periarthritis Nodosa. *Bull New York Med Coll & Fifth Ave Hosp* 7:94, 1944.
- BRADSHAW, H. Periarthritis Nodosa Limited to the Pulmonary Circulation. *Am J Path* 51:837, 1955.
- CAKINS, C., and BAUER, W. The Protean Manifestations of the Connective Tissue Diseases. *M Clin North Am* 39:375, 1955.
- CAREY, R. A., HARVEY, A. M., and HOWARD, J. C. The

- Effect of Adrenocorticotrophic Hormone (ACTH) and Cortisone on the Course of Disseminated Lupus Erythematosus and Periarthritis Nodosa. *Brit Jolin Hopkins Hosp* 87:475 1950
- CHURCH J and STRAUSS L Allergic Granulomatosis Allergic Angitis and Periarthritis Nodosa. *Am J Path* 77:277 1951
- DOLB H P, GOODRICH R E, and GISH J R The Pulmonary Aspects of Polyarteritis (Periarthritis) Nodosa. *Am J Roentgenol* 71:785 1954
- EDWARDS J E, PARAIN T W, and BURCHIELL H B Recurrent Hemoptysis and Necrotizing Pulmonary Abscess in a Patient with Acute Glomerulonephritis and Periarthritis Nodosa. *Proc Staff Meet., Mayo Clin* 39:193 1954
- ELMICH J C and ROMANOFF A Allergic Granuloma of the Lung: Clinical and Anatomic Findings in a Patient with Bronchial Asthma and Eosinophilia. *Arch Int Med* 87:759 1951
- ELKES A, and GLENN L E Serial Roentgenograms of the Chest in Periarthritis Nodosa as an Aid to Diagnosis. *Brit J Radiol* 17:168 1944
- ELMAN P, and CLOBOVIC L Pulmonary Manifestations of the Diffuse Collagen Diseases. *TThorax* 9:46 1954
- FABRY J L, LEONARD E, CHURG J, and GOODMAN G Wegener's Granulomatosis. *Am J Med* 17:168 1954
- FRIEDBERG, R Necrotizing Granulomatosis and Angitis of the Lungs and Its Relationship to Chronic Pneumonitis of the Cholesterol Type. *Am J Path* 29:913 1951
- GARLAND L W, and SISSON M A Roentgen Findings in the Collagen Diseases. *Am J Roentgenol* 71:181 1954
- GOLDMAN R, ADAMS W S, BEEK W S, LEVIN M, BASSETT S H, and WHITE A The Effect of ACTH in One Case of Periarthritis Nodosa. In: *Worke, J R Proceedings of the First Clinical ACTH Conference*. Philadelphia: The Blakiston Company 1950 p 417
- GURRICH G C, and VETAL L L Polyarteritis Nodosa: A Correlation of Clinical and Postmortem Findings in Seventeen Cases. *Circulation* 34:81 1951
- GUTER G B Zur Frage der Periarthritis nodosa in der sonderer Berücksichtigung der Gallenblasen und Nieren Beteiligung. *Wiener Arch Path Anat* 78:441 1951
- HARRIS A W, LYONS G W, and O'HARA J P Periarthritis Nodosa. *Arch Int Med* 63:1165 1949
- HARRIS A W, G Pulmonary Changes in a Case of Periarthritis Nodosa. *Am J Roentgenol* 70:607 1953
- HOS J D Acute Arterial Necrosis in the Lungs. *J Pathol & Bact*, 61:333 1953
- KAMPMACHER H H, and SHAPIRO J L Diffuse and Sometimes Recurrent Course of Diffuse Arteritis. *Arch Int Med* 97:815 1953
- KLEIN M P Periarthritis Nodosa: Study of Chronicity and Recovery in the Report of Two Cases. *Arch Int Med* 84:983 1949
- KLEMPERER P Concept of Collagen Diseases. *Am J Path* 76:505 1950
- KROWLER J C, JR, ZEEK P W, and BLANCKENHORN M A Studies of Necrotizing Angitis in Periarthritis Nodosa and Hypersensitivity Angitis. *Arch Int Med* 97:789 1953
- KUSMALL, A, and MATZ R Über eine bisher nicht beschriebene eigenartige Arterienkrankung (Periarthritis nodosa) die mit Morbus Brighti und rapid fortschreitender allgemeiner Muskellähmung einhergeht. *Deutsches Arch klin Med*, 1484 1866
- LABB E, SHAWER Z, and SCHORR S Periarthritis Nodosa in a Nine-month-old Infant. *Am J Dis Child* 88:10 1954
- LINCOLN M, and RICKES W A A Case of Periarthritis Nodosa with I E Cells: Apparent Complete Remission with Cortisone Therapy. *Ann Int Med* 41:639 1954
- LOCKE, R B, and MELLINS F Polyarteritis Nodosa: Report of 11 Cases with Review of Recent Literature. *Ann Int Med* 24:11 1946
- LYALL A Periarthritis Nodosa. *Lancet* 2:973 1954
- MELTZOW W M Allergic Granulomas of the Prostate Gland. *J Urol* 65:188 1951
- MILLER H G, and DALEY R Clinical Aspects of Polyarteritis Nodosa. *Quart J Med* 15:255 1946
- OPPEL W Periarthritis acuta nodosa. *Arch Int Med*, 17:870 1973
- PARRIN T W, RUSTED I E, BURCHIELL H B, and EDWARDS J E Hemorrhagic and Intermittent Pneumonitis with Nephritis. *Am J Med* 18:770 1955
- RIGBY C, FELDMAN H A, CLARK W S, FINGERT, E E, LOWMAN E, McEWEN C, ZIFF W, HOLLANDER J L, and JESSAR R A Primer on the Rheumatic Diseases. *J A M A* 157:321 405 572 1953
- RICH A R, and GRACOV J E The Experimental Demonstration that Periarthritis Nodosa is a Manifestation of Hypersensitivity. *Brit Jolin Hopkins Hosp* 72:65 1943
- ROSE W H, LITVINSON D, and HOLSTON J Polyarteritis Nodosa: A Clinical and Pathological Study and Report of Six Cases. *Ann Int Med*, 37:1114 1950
- SILVER B P, MATTHEWS J H, and BORSTEIN S Pulmonary Cavitation Due to Polyarteritis. *J A M A* 144:754 1950
- SHICK R M, BACCANROSS A H, FULLER B F, and POLLEY H F Effects of Cortisone and ACTH on Periarthritis Nodosa. *Ann Med* 34:851 1951
- SPITZBERG D L Vitamin E and Collagen in Rheumatic Diseases. *Ann New York Acad Sci* 52:380 1949
- SPITZBERG, T Roentgenographic Pulmonary Changes in Periarthritis Nodosa. *Acta Radiol* 26:307 1945
- SWEENEY A R, JR, and BACCANROSS A H Pulmonary Lesions of Periarthritis Nodosa. *Proc Staff Meet Mayo Clin* 24:35 1949
- WEGENER F Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterienstroms und der Nieren. *Beitr path Anat u allg Path*, 107:36, 1939
- LEEN P M Periarthritis Nodosa: A Critical Review. *Am J Clin Path* 27:777 1952
- LEEN P M, SMITH C C, and WALTER J C Studies on Periarthritis Nodosa: Differentiation of Periarthritis Nodosa and of Hypersensitivity. *Am J Path* 24:689 1949

RHEUMATIC PNEUMONIA

- FILCO B M Allergic Inflammation of the Lungs. *Arch Path*, 18:865 1934
- FRIEDBERG, C K, and GROSS L Periarthritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease. *Arch Int Med*, 54:10 1934

- GOLLEY, H. A. The Acute and Subacute Pulmonary Involvement in Rheumatic Fever with Notes on the Complication of Basal Pulmonary Collapse *Ann Int Med*, 11 626, 1937
- GREGORY, J. E., and RICH, A. R. The Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis *Bull Johns Hopkins Hosp*, 78 1, 1946
- LEVY, H. B., COFFEY, J. D., and ANDERSON, C. E., JR. Rheumatic Pneumonitis in Childhood *Pediatrics*, 2:688, 1948
- MCCLENNAN, W. U., and PAUL, J. R. A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever *Arch Path*, 8 595, 1929
- MURHEAD, E. E., and HALEY, A. L. Rheumatic Pneumonitis *Arch Int Med*, 80 328, 1947
- NEUBERGER, K. T., GREYER, E. F., and RUTLEDGE, E. K. Rheumatic Pneumonia *Arch Path*, 37 1, 1944
- SELDIN, D. W., KAPLAN, H. S., and BUNTING, H. Rheumatic Pneumonia *Ann Int Med*, 26 496, 1947
- Auswertung für des ärztliche Rheumaproblem *Ergebn allg Path u path Anat*, 27 1, 1933
- LEES, A. W. Acute Polyarthritides with Pulmonary Consolidation and Pleural Effusion *Brit M J*, 1 246, 1952
- LEYS, H. G., and SWIFT, P. N. Pulmonary Lesions in Rheumatoid Arthritis *Brit M J*, 1 434, 1949
- WIALA, W. E., CAPLAN, A., COCHRANE, A. L., KILPATRICK, G. S., and OLMIAN, P. D. An Epidemiological Study of Rheumatoid Arthritis Associated with Characteristic Chest X Ray Appearances in Coal Miners *Brit M J*, 2 131, 1953
- MURHEAD, E. E., and HALEY, A. L. Rheumatic Pneumonitis *Arch Int Med*, 80 328, 1947
- ROBINSON, W. D., et al. Rheumatism and Arthritis Tenth Rheumatism Review *Ann Int Med*, 39 498, 257, 1953
- ROSENBERG, C. F., BAGGENSTOSS, A. H., and HENCH, P. S. The Cause of Death in Thirty Cases of Rheumatoid Arthritis *Ann Int Med*, 20 903, 1944
- YOUNG, D., and SCHWEDER, J. B. The Heart in Rheumatoid Arthritis *Am Heart J*, 28 1, 1944
- ### PULMONARY LESIONS IN "RHEUMATOID DISEASE"
- ALEPBAUGH, S. A., MINIS, O. M., and GOODPASTURE, E. W. Pulmonary Fibrosis Secondary to Pneumonia *Am J Path*, 28 69, 1952
- BAGGENSTOSS, A. H., and ROSENBERG, C. F. Visceral Lesions Associated with Chronic Infectious (Rheumatoid) Arthritis *Arch Path*, 35 503, 1943
- BERGSTRAND, H. Morphological Equivalents in Polyarthritides Rheumatica, Periarthritis Nodosa, Transient Eosinophilic Infiltration of the Lung and Other Allergic Syndromes *J Path & Bact* 58 399, 1946
- BEVANS, M., NADELL, J., DEMARTINI, F., and RAGAN, C. The Systemic Lesions of Malignant Rheumatoid Arthritis *Am J Med*, 16 197, 1954
- BLOOM, J., and REAIN, J. H. Transient Pulmonary Manifestations in Rheumatoid Arthritis *Canad M A J*, 63 355, 1950
- CAPLAN, A. Certain Unusual Radiological Appearances in the Chest of Coal-Miners Suffering from Rheumatoid Arthritis *Thorax*, 8 29, 1953
- CHRISTIE, G. S. Pulmonary Lesions in Rheumatoid Arthritis *Australian Ann Med* 3 49, 1954
- ELLMAN, P. The Etiology of Chronic Rheumatism *Proc Roy Soc Med*, 46 332, 1946
- ELLMAN, P., and BALL, R. E. "Rheumatoid Disease" With Joint and Pulmonary Manifestations *Brit M J*, 2 816, 1948
- GREGORY, J. E., and RICH, A. R. The Experimental Production of Anaphylactic Pulmonary Lesions with the Basic Characteristics of Rheumatic Pneumonitis *Bull Johns Hopkins Hosp*, 78 1, 1946
- GREENWALD, P. Visceral Lesions in a Case of Rheumatoid Arthritis *Arch Path*, 45 59, 1948
- HARRIS, L. H. Pulmonary Manifestations of Rheumatoid Disease *Lancet*, 2 119, 1954
- KATZ, H. L., and ALTBACH, O. Diffuse Interstitial Fibrosis of the Lungs *Dis Chest*, 20 366, 1951
- KUNZE, F. Der Rheumatismus, Pathologisch-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für des ärztliche Rheumaproblem *Ergebn allg Path u path Anat*, 27 1, 1933
- ### DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS HAMMAN-RICH SYNDROME
- ALEPBAUGH, S. A., MINIS, O. M., and GOODPASTURE, E. W. Pulmonary Fibrosis Secondary to Pneumonia *Am J Path*, 28 69, 1952
- AUSTRIAN, R., MCCLEMENT, J. H., RENZETTI, A. D., JR., DONALD, H. W., RILEY, R. L., and COURAND, A. Clinical and Physiologic Features of Some Types of Pulmonary Diseases with Impairment of Alveolar capillary Diffusion The Syndrome of Alveolar capillary Block *Am J Med*, 11 667, 1951
- CALLAHAN, W. P., JR., SUTHERLAND, J. C., FULTON, J. K., and HILKE, J. R. Acute Diffuse Interstitial Fibrosis of the Lungs *Arch Int Med*, 80 468, 1952
- GREYER, E. F., NEUBERGER, K. T., and DAVIS, C. L. The Pulmonary Alveolar Lining Under Various Pathologic Conditions in Man and Animals *Am J Path*, 19 913, 1943
- GOLDEN, A., and TULLIS, J. F., JR. Diffuse Interstitial Fibrosis of the Lungs *Mil Surgeon*, 105 130, 1949
- HAMMAN, L., and RICH, A. R. Acute Diffuse Interstitial Fibrosis of the Lungs. *Bull Johns Hopkins Hosp*, 74 177, 1944
- KNEELAND, A., JR., and SMETANA, H. F. Current Bronchopneumonia of Unusual Character and Undetermined Etiology *Bull Johns Hopkins Hosp*, 67 229, 1940
- MACMILLAN, J. M. Familial Pulmonary Fibrosis *Dis Chest*, 20 426, 1951
- OGILVIE, A. G., and HULSE, E. V. Some Observations on a Case of Diffuse Interstitial Fibrosis of the Lungs *Brit J Tuberc*, 48 200, 1954
- PEARSON, J. W., PEARSON, J. W., JR., and HAYES, F. W., and HAYES, E. W., JR. Idiopathic Pulmonary Fibrosis Its Occurrence in Identical Twin Sisters *Dis Chest*, 19 310, 1950
- REBER, E. H. Pulmonary Lesions in "Rheumatoid Disease" with Remarks on Diffuse Interstitial Pulmonary Fibrosis *Am J Med*, 19 569, 1955

- Rebin, E. H., Kahn, E. S., and Pecker, D. Diffuse Interstitial Fibrosis of the Lungs *Ann Int Med*, 36 827, 1952
- Rebin, E. H., and Lubliner, R. Diffuse Interstitial Fibrosis of the Lungs In Preparation
- Schachter, M. M. Diffuse Interstitial Fibrosis of the Lungs *Am Rev Tuberc*, 63 601, 1951
- Wildebecker, H. L., and Barclay, W. R. Diffuse Interstitial Pulmonary Fibrosis *Ann Int Med*, 41 1127, 1955
- Zimmerman, H. M. Personal Communication

Diseases of the Skin and Mucous Membranes

Introduction

IT IS A MATTER of common knowledge that metabolic, allergic, infectious and malignant diseases of internal organs may affect the skin. Less widely known is the fact that there are a sizable number of diseases with predominant localization in the skin and mucous membranes which also find expression in deeper organs and tissues of the body. Of particular interest, from the view point of the present discussion, are the pulmonary manifestations appearing at the inception of certain skin diseases with every indication that the changes in the lungs represent an integral part of a systemic disease. As a rule, little attention is paid to the pulmonary findings in skin diseases unless the former are pronounced. Either no abnormal signs are elicited on physical exploration of the chest or else the condition of the skin may be in a state as to preclude a thorough examination. At best the pulmonary involvement is recognized only when a complicating pneumonia supervenes or as a terminal event in the course of a chronic debilitating illness.

In the usual type of skin disease, encountered in office and clinic practice a chest x ray is seldom considered necessary and as a result much important information which might be obtained

by this means does not come to light. Yet, there is evidence that even in apparently superficial skin diseases the internal organs may be implicated. Discerning dermatologists have for years stressed the fact that few skin diseases are skin deep. Physicians have long been aware of the fact that the skin is a sensitive barometer in health and disease and often serves as a mirror of disease of internal organs. Of late, increasing interest is also being directed to the reverse of the image—the lungs as a mirror of skin disease.

As a point of historical interest, Keil draws attention to the fact that Osler, as early as 1888 and in later communications, suggested that in certain systemic diseases notably the erythema group, alterations occurring in the skin have their counterpart in internal organs. In some, the visceral manifestations precede the cutaneous ones. A classical example of this interrelationship, and with which Osler's name is associated is hereditary hemorrhagic telangiectasis. We have learned since that systemic lupus erythematosus, sarcoidosis and several other conditions to be described later, which were at one time considered dermatologic disorders may, in fact, never reveal themselves in the skin during the entire course of the disease.

Allergic Dermatitis

Fleeting pulmonary infiltrations associated with eosinophilia may punctuate the course of acute and chronic allergic diseases involving the skin. The dermatologist seldom gives thought to the lungs unless there is a complicating pneumonia, the physician interested in chest diseases is unlikely to have an opportunity to see such

patients because, as a rule, there are no symptoms or signs referable to the lungs, and the roentgenologist, knowing little of the patient's history and dermal condition is apt to be at a loss to explain the abnormal roentgen findings as illustrated by the following experience.

An elderly man had been convalescing from

an acute pneumonia. Repeated chest x-rays during the illness had shown progressive resolution of the process. Shortly before the patient was scheduled for discharge, a chest x-ray was taken to make certain the lungs were clear. The patient's physician was hurriedly called by a disturbed roentgenologist and told that the film revealed pulmonary infiltrations, probably representing military tuberculosis. When I saw the patient, the latter was up and about feeling quite well but complaining of itching of the skin which was associated with an erythematous rash of the face, chest and upper extremities. The condition was obviously a late hypersensitivity reaction to the penicillin which the patient had been receiving. The finding of eosinophilia in the blood and the rapid disappearance of the pulmonary infiltrations, coincidentally with the subsidence of the skin eruption, confirmed this belief.

On another occasion, I had occasion to see a young woman of twenty-one who had been under treatment for a severe form of neurodermatitis and seborrheic dermatitis. Patch tests revealed positive reactions to various contactants. Repeated chest x-rays had failed to reveal any abnormalities. Several blood examinations had shown nothing unusual, the eosinophil count averaging 1 per cent. On one occasion the patient developed fever and chest pain. A chest x-ray revealed irregular infiltrations in the lower portions of both lungs and accentuation of the hilar markings. Blood counts at this time showed a moderate leukocytosis with 10 per cent eosinophils, subsequent counts revealed an eosinophilia as high as 16 per cent. The sputum also contained eosinophils but no acid fast organisms. The infiltrations disappeared gradually and the lungs resumed their previous state.

Frostberg relates the case of a twenty-six year old woman who was treating herself with mercury ointment for scabies. The patient developed an acute dermatitis with fever, rapid pulse and leukocytosis, no eosinophilia. Chest x-rays disclosed reticular markings in both lower lung fields. With the fading of the exanthem, the roentgenogram resumed its original configuration. Prompted by this experience, Frostberg had routine chest x-rays taken of all patients with

acute generalized dermatitis where 'the clinical findings were of such a nature that lung involvement might be suspected'. In less than a year, Frostberg encountered a man of forty with an intense dermatitis, probably due to barbiturate medication. The chest x-ray revealed mottled and reticular densities. In addition, there was an eosinophilia of 12 per cent. The infiltrations cleared with the disappearance of the exanthem. As in the first case, there were no clinical signs referable to the respiratory tract. The roentgen findings were ascribed in both instances to a hypersensitivity reaction in the lungs of a type seen in Loeffler's syndrome. Two similar experiences were reported by Falk and Newcomer. The cause of the fleeting pulmonary infiltrations in their cases was believed to be in an allergenic penicillin-oil wax preparation which was being administered for early syphilis.

Reference was made in Chapter 5 to, so-called, 'creeping eruption' of the skin, endemic in the Southeastern coastal regions of the United States, which may be associated with Loeffler's syndrome. In 1917, Kirby Smith suggested a nematodal origin of the disease and, in 1926, with Dove and White, proved this to be the case. Wright and Gold were the first to describe the association of cutaneous helminthiasis with Loeffler's syndrome. It appears that the infection with the filariform larvae of the *Anclystomus braziliense* (hookworm of dogs and cats) occurs most frequently on beaches and under houses. The disease is there fore apt to be contracted by swimmers, children, painters, carpenters and termite exterminators. The larval form of the nematode, when it comes in contact with the skin, loses its cutaneous sheath and penetrates the skin. A small papule develops at the site of penetration and soon scirpigenous, elevated burrows appear, the urticarial like lesion being associated with considerable itching. Wright and Gold were unable to find *Anclystomus* ova in a single instance of 441 stool examinations made in a series of seventy-six cases. Nevertheless, Loeffler's syndrome was encountered in twenty-six. These investigators therefore concluded that the pulmonary infiltrations were caused by an antigenic response to the presence

of either the larvae or the blood borne exotoxin. However, the possibility of the pulmonary infil-

trations being caused by transpulmonary larval migration cannot be excluded.

Erythema Multiforme

This disease is characterized by pleomorphic changes in the skin, chiefly of the extensor surfaces of the limbs consisting of erythema, papules and/or vesicles and bullae. The seasonal incidence and, at times, epidemic occurrence of the disease, the febrile systemic manifestations, the mononuclear and nonbacterial character of the exudate, and the simultaneous development in some cases of atypical pneumonia, point to a generalized inflammation. If the disease is caused by a single agent, it is most likely due to a virus. Finland and co-workers obtained positive complement fixation tests for psittacosis in two cases and a positive cold agglutination test in one. Increasing numbers of investigators are subscribing to the belief that the disease, at least in some patients, is of allergic nature caused by hypersensitivity to drugs or bacterial or viral products. A feature of one form of erythema multiforme is the occurrence of stomatitis, conjunctivitis and balanitis, occasionally in association with pneumonia. This syndrome is variously described as "eruptive fever," "mucosal respiratory syndrome," "Stevens-Johnson syndrome" and by several other eponyms.

Keil was among the first to draw attention to the fact that erythema multiforme may be associated with simultaneous involvement of the trachea, bronchi and lungs. In fact Hebra who coined the term 'erythema multiforme exudativum,' referred in his classic *Diseases of the Skin* published in 1866, to a case complicated by pneumonia. The prominence of the respiratory tract involvement and the integral part which this system plays in erythema multiforme is stressed in a publication by the Commission on Acute Respiratory Diseases created during World War II. The report includes case histories of six patients, three of whom had atypical nonbacterial pneumonias. Finland and co-workers reported six cases of erythema multiforme associated with pneumonia. Stanjon and Warner observed seventeen military personnel with striking skin and mucosal lesions, fourteen of whom had pul-

monary involvement at sometime during the course of the disease.

The onset of the disease is usually abrupt following a short prodromal period. In many the onset is ushered in by an upper respiratory infection with fever, malaise, sore throat, cough and other symptoms commonly encountered in influenza. In an analysis of twenty patients personally observed, and twenty-two collected from the literature, Soll found twenty-nine (69 per cent) to have had prodromal respiratory symptoms. The malignant form of erythema multiforme as noted by Costello, is particularly apt to be associated with pneumonia. At the height of the disease, pain in the eyes, photophobia, difficulty in swallowing, high fever, cough, delirium and prostration may reach alarming proportions. In the majority there is rapid clearance, in some, the disease pursues a fatal course.

Pneumonia occurring in association with erythema multiforme closely resembles that seen in the primary atypical variety. An unusually instructive case was presented by Markham at a clinical meeting of the Kingston Garrison Medical Society. The particular patient developed signs and symptoms of what seemed to be an atypical pneumonia. Shortly after the onset of the disease there appeared a severe conjunctivitis, a membranous eruption of the mucous membranes of the mouth, a bullous skin eruption and balanitis. Several other cases have been described in which the pneumonia and skin manifestations appeared simultaneously. But, in view of the fact that in some of the cases there were no antecedent x-rays of the chest available, the pulmonary involvement may have been present but was unrecognized before the eruptive changes in the skin took place.

The pulmonary findings in patients with erythema multiforme are best appreciated in serial chest x-rays taken during the course of the disease. In the majority, one encounters a simple bronchitis in association with the acute mucosal lesions of the mouth, larynx and pharynx with-

our demonstrable involvement of the lungs. In others the chest x-rays reveal changes in the lungs consisting either of (1) miliary or nodular densities simulating tuberculosis (2) scattered patchy infiltrations in one or both lungs such as one encounters in bronchopneumonia (3) massive pneumonic consolidations and (4) on rare occasions a complicating pleuritic effusion. The postmortem findings as might be expected represent a summation of tissue changes caused by superimposed infection in association with acute congestion and suppuration.

Since treatment of pneumonia with sulfonamides and other drugs may cause skin eruptions one has to be on guard when using such drugs not to confuse toxic skin reactions with erythema multiforme. In any event sulfonamides, penicillin and aureomycin have little effect on the disease itself although they do help control secondary infection. Yates and co-workers also Agostas and co-workers obtained favorable immediate results with ACTH and cortisone treatment. Since most cases recover without treatment one has to maintain a critical attitude of the value of therapeutic agents. However further exploration with the use of ACTH and cortisone is indicated.

Erythema Nodosum

According to Beerman erythema nodosum is an example of the intangible borderline between dermatology and internal medicine. Erythema nodosum is a self limited disease of a few weeks duration. The skin lesions are characterized by the appearance of discrete red tender nodules of varying size in the subcutaneous tissues especially of the forearms and legs. The nodules may appear in crops. The eruption is often preceded by a febrile episode sometimes chill also sore throat joint pains and constitutional symptoms. After the subsidence of the acute stage the nodules gradually change in appearance to a dark red then a brick color a yellowish pigmentation persisting in the skin for sometime after the disappearance of the lesions. Histologically the nodules are composed of fibroid degeneration of connective tissue septa granulomatous foci of histiocytes and lymphocytes with occasional giant cells of the foreign body type.

The cause of erythema nodosum has been a subject of discussion for many years. Earlier observers considered the condition a specific disease a belief which persisted until quite recently. The hypothesis of the specificity of erythema nodosum became less tenable as increasing numbers of conditions were found associated with a similar skin eruption. In a significant percentage of cases especially in the Scandinavian countries and in England erythema nodosum has been found in association with recent tuberculous infections. Of late the view is becoming more widespread that erythema nodosum is a nonspecific allergic reaction to a variety of bacterial chemical and toxic agents. Special attention has been directed to infections associated with *B. hemolyticus streptococci coecidiodomycosis* and *sulfonamide* medication. Lofgren and Wahlgren concluded from a study of sixty four cases that the histological picture is in keeping with an allergic skin eruption. With increasing use of routine chest roentgenography large numbers of cases are found without any associated diseases.

The intrathoracic manifestations of erythema nodosum concern chiefly often exclusively the hilar lymph nodes. However the lung parenchyma may be involved without roentgenographic participation of the lymph nodes. In children there is apt to be a unilateral density extending fanwise from the hilus into the adjacent parenchyma (Figure 28A). In adults the hilar tumor is larger usually bilateral and the lung parenchyma is more likely to be involved (Figure 28B). Of particular interest from the viewpoint of differential diagnosis is the striking resemblance roentgenologically of erythema nodosum and sarcoidosis. In fact Kerley found that approximately 25 per cent of the patients with sarcoidosis had a history suggestive of erythema nodosum. It might be mentioned that many investigators make no distinction between the two conditions and ascribe both to manifestations of hypersensitivity.

Lofgren in Scandinavia found pulmonary



Figure 28 Erythema nodosum with intrathoracic lesions. A (Left) Prominent hilar densities, more marked on left (in a boy of ten years) B (Right) Bilateral, prominent hilar densities (in a man of twenty one years)

changes of fresh appearance, at the first roentgenographic examination after the skin eruption, in 78 per cent of 178 cases of erythema nodosum. The incidence of unilateral glandular enlargement showed a direct relationship to the degree of tuberculin sensitivity but in the presence of bilateral lymph node involvement the reverse was true. In the presence of bilateral hilar adenopathy, a considerable number were found to represent sarcoidosis. Johnson and his co-workers believe that if evidence of hilar adenopathy is found in the chest x-ray of a case of erythema nodosum the hilar enlargement is simply part of a disease of nonspecific etiology. It is a common experience for one to find accidentally in chest x-rays bilateral hilar lymph node enlargement and in many instances a cause cannot be found. By 'rule-of thumb,' unilateral

hilar lymph node enlargements in children with positive tuberculin skin tests is assumed to be caused by tuberculosis, bilateral lymph node enlargement with negative tuberculin skin tests in adults is assumed to be sarcoidosis.

Hodgson and co-workers list the following conditions which may be associated with bilateral hilar adenopathy: (1) tuberculosis, (2) BCG vaccination, (3) infections, histoplasmosis and coccidioidomycosis, (4) sarcoidosis, (5) pneumoconiosis, (6) lymphogranuloma venereum, (7) secondary syphilis, (8) neoplasms, Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and leukemia, (9) metastatic malignant growths of the lung and elsewhere, (10) conditions associated with erythema nodosum and (11) fibrocystic disease of the pancreas.

Disseminated Lupus Erythematosus

INTRODUCTION

'Lupus erythematosus, erythema nodosum and sarcoidosis, all diseases which historically were dermatologic conditions have, with the advances in diagnosis become important entities which are the concern of all diagnosticians' (Michaelson). In fact, as increasing numbers of patients with

systemic lupus erythematosus are being recognized, internists are gradually usurping this intriguing disease from dermatologists and adopting it as their own. The LE test, now widely used in diagnosis, as well as the recent introduction of cortisone and corticotropic hormonal treatment, have served to popularize the disease among phy-

sicians at large. Disseminated lupus erythematosus, at one time considered a rarity, is now being diagnosed with considerable frequency. Du Bois reported that in the years 1948 and 1949 the diagnosis was made eleven times in the Los Angeles General County Hospital. But after the hospital staff became "lupus conscious," a total of forty-four cases were diagnosed in the following two years.

The systemic manifestations of lupus erythematosus were described by Kaposi in 1872 and by Jadassohn early in the present century. It is more likely, however, as suggested by Klemperer, that the observations of these investigators refer red primarily to the toxic symptoms of the cutaneous involvement. Older dermatologists recognized a localized, discoid form now believed to be only one of the manifestations of the disease. Keil is largely responsible for dissociating lupus erythematosus from tuberculosis—a belief once widely held—attested by the name which bears no relation to the true nature of the disease. Keil also pioneered in the concept that a number of skin diseases including disseminated lupus erythematosus, are only outward manifestations of more profound disturbances affecting deeper organs and tissues of the body.

CLINICAL FEATURES

Disseminated lupus erythematosus affects chiefly females, especially those of the second and third decades of life. Red-haired young women with a tendency to freckling of the skin are especially vulnerable. The appearance of the skin is characterized by a butterfly erythema on the bridge of the nose and cheeks which is sensitive to light, drugs and irritants of any type. Older lesions may show atrophy, telangiectasis and pigmentation but some doubt that these changes are in reality lesions of disseminated disease. Aberrant forms are not uncommon. Cutaneous lesions may be absent or they may appear late in the disease.

Systemic involvement is associated with fever, joint manifestations of varying severity, lymph node enlargement and a prolonged remissive course. The disease is almost invariably fatal; however, individual cases have been reported

where the disease had lasted twenty years and longer. The endocardium, kidneys, bone marrow and serous membranes are often implicated producing their own train of symptoms and signs. Laboratory procedures of value in diagnosis include a leukopenia with a uniform reduction of all the white cells, a rapid blood sedimentation, an inversion of the albumin-globulin ratio, the hyperglobulinemia being made up chiefly of the gamma fraction. The latter is believed to cause an occasional false positive serological reaction for syphilis, a phenomenon in itself of diagnostic significance.

The presence of inclusion bodies, so called "LE cells," in the peripheral blood and bone marrow is invaluable as a diagnostic aid. The important work leading to the discovery of the test was begun by Hargraves and developed further by Hasenick and others. The "LE cell" is a polymorphonuclear leukocyte which contains a mass of ingested nuclear material and gives staining reactions identical with those of the haematoxylin staining bodies found in the viscera. Klemperer and co-workers identified the material as depolymerized desoxyribonucleic acid and related it structurally to the inclusion bodies of the LE cell. Hargraves correlates the LE phenomenon with blood coagulation, especially the blood platelets and their disintegration products. LE inclusion bodies in disseminated lupus erythematosus may be demonstrated in sternal marrow as well as in peripheral blood. Hasenick obtained positive LE tests in twenty-two patients, fifteen of whom had no skin eruption at the time of the positive test, six of these developed later a typical erythema.

The LE phenomenon has been claimed by some to be pathognomonic of the disease. However, cases have been reported in which LE cells have been found in dermatitis herpetiformis, diffuse interstitial fibrosis of unknown cause, in an appreciable number of rheumatoid arthritis, polyarteritis nodosa, miliary tuberculosis during cortisone withdrawal, hydralazine toxicity, scleroderma, leukemia, pernicious anemia in relapse and multiple myeloma. A significant number of false positive tests have been reported in association with severe hypersensitivity reactions to

penicillin. According to Cohen, this may provide a link between this disease and polyarteritis nodosa whose relationship to drug sensitivity is well established. The occurrence of LC cells in association with hypersensitivity is suggestive that the phenomenon may be related to an immunologic mechanism. In this respect it might be mentioned that the reported finding of LC cells in some cases of pleural effusions of undetermined etiology is also in keeping with hypersensitivity. It should be noted that not infrequently a pleural effusion heralds the appearance of disseminated lupus erythematosus. In general, the specificity of the LC phenomenon in acute disseminated lupus erythematosus is of such high order that it is good practice to utilize the test routinely in every unexplained febrile or undiagnosed systemic disease. The LC test is also of considerable prognostic value because it permits the evaluation of results of treatment as well as being a useful tool in studying the mechanism of the disease. It should be noted, however, that if careful search is made LC cells are usually found in patients under most effective steroid treatment. Apparently the basic disturbance is not greatly altered by medication.

PATHOLOGY

The pathological changes in disseminated lupus erythematosus are essentially of a two fold nature (1) those referable to vascular involvement, and (2) those referable to fibrinoid degeneration of connective tissue. The involvement of blood vessels interferes with fluid interchange and affects not only the systemic circulation but also, at times the pulmonary circulation. The vascular changes may consist of simple dilatation of the capillary bed or proliferative lesions of the lining epithelium of the capillaries, arterioles and venules. The changes are often associated with thrombi and occasionally occlusion of vessels, there are also degenerative and necrotizing lesions. Fibrinoid degeneration of the connective tissues of the mesenchymal organs results in fragmentation of these elements, swelling and increased density of the interfibrillar ground substance, eventually resulting in sclerosis. These features are shared

to variable degrees by polyarteritis nodosa, vasculitis of rheumatic fever, scleroderma, dermatomyositis and several others of, the so called collagen group of diseases.

PULMONARY LESIONS

The pleuropulmonary manifestations of systemic lupus erythematosus have received little attention possibly because the lungs do not show as striking features of the disease as do the heart, kidneys, joints and hemopoietic organs. Yet, there is hardly a patient with acute systemic lupus erythematosus who does not have, at one time or another, involvement of the lungs especially of the pleura. The pleural involvement may be recurrent affecting one cavity or the other. It may be of a dry fibrinous variety or appear as an effusion of moderate or massive proportions. Tumulty found that if the effusion is massive it may herald secondary infection. He also found tuberculosis not an uncommon complication. Suppurative bronchopneumonia is also frequently encountered.

In occasional instances one meets with patients who have recurrent unexplained respiratory tract infections, with or without gross evidence of pneumonia, long before the true nature of the disease becomes clinically apparent. There is every reason to expect that a disseminated disease, such as lupus erythematosus, with a predilection for vascular structures, connective tissue and serous membranes, should find the lungs and pleura favorable sites for development. In a study of 105 patients with systemic lupus erythematosus, Tumulty was impressed with the frequency and importance of the pulmonary involvement. This investigator observed two types of alterations: those due to the lupus itself and those due to secondary bacterial infection. The involvement of the lung by lupus, according to Tumulty, is often overlooked or considered to be a pneumonia of bacterial or viral origin. The basal portions of the lungs are most vulnerable, a prominent feature being connective tissue organization of alveolar spaces resulting in small patches of atelectasis.

The symptoms and signs of pleuropulmonary involvement in systemic lupus erythematosus in-

clude cough chest pain dyspnea bloody sputum and gross hemoptysis. The bloodspitting may be due to the acute arteritis of the pulmonary blood vessels or to cavitation resulting from anemic necrosis of affected lung tissue. A pleural friction rub is often heard and there is early appearance of fluid in the pleural cavity often on both sides. Occasionally the fluid is hemorrhagic the blood probably originating in perichiae of the pleural cavity. Jessar and co-workers analyzed the symptomatology of a collected group of 279 patients with disseminated lupus erythematosus during the years 1948 to 1957. They found in their own cases manifest pleural effusion in 39 per cent pleural rub in 20 per cent and pneumonitis in 70 per cent. In the collected series, symptoms or signs referable to the respiratory tract were recorded in 38 per cent including pleural effusion in 79 per cent. The authors overlooked to a fact one which is often approximated in an given group of patients greater than five years from the onset of the disease.

In an analysis of eighteen autopsied cases of disseminated lupus erythematosus including one of their own the Reisensteins found pleuritis with or without effusion a constant feature. They noted that it is common for signs of pulmonary involvement to be present for many months during the course of the disease. Thirteen of the eighteen cases had pulmonary consolidation and an additional four congestion or partial collapse of the lungs. In most instances the consolidation was of a patchy nature in a few it was lobar Griffith and Loral in a similar study of eighteen autopsied cases found abnormalities in the lungs and pleura in every one.

Purnell and co-workers studied the pulmonary lesions of lupus erythematosus in fifty-four patients examined at autopsy. In more than half bronchopneumonia hemorrhagic pleural effusion edema interstitial pneumonia or congestion often a combination were demonstrable. Likewise Klempner Pullack and Bachr in a study of the autopsy findings in twenty cases noted that the postmortem changes do not proceed

erly reflect the remarkable clinical manifestations of the pulmonary involvement in this disease—the long bouts of waning and waning migrating bronchopneumonia. These investigators draw attention to the serous membrane involvement in this disease which is characterized by strikingly thick gelatinous and succulent tissue. Humphreys was likewise impressed by the loose gelatinous fibrous adhesions often seen in the pleural spaces of patients with systemic lupus erythematosus.

Particularly instructive from the viewpoint of pleuropulmonary involvement are reports of individual patients followed for long periods. Rakov and Taylor reported an instance of systemic lupus erythematosus in which the dominant feature of the disease was a long continued consolidation of the lungs which appeared early in the course of the disease and persisted for eight months until death. The authors considered the pulmonary involvement an integral part of the disease. The postmortem examination revealed lobular consolidation with intervening air containing alveoli surrounded by thickened alveolar septums also a low grade chronic inflammation consisting almost entirely of large mononuclear cells. The greatly thickened pleural surface of the lung was made up of fibrous tissue which was highly vascular and still the seat of a fairly intense inflammation also consisting almost entirely of mononuclear elements.

Baggenstoss noted in his cases a peculiar basophilic mucinous edema in the connective tissue of the alveolar walls and in the peribronchial and perivascular tissues. This finding was noted in nine of fifty-four patients examined at autopsy and usually in association with interstitial pneumonitis and alveolar hemorrhage. The mucinous interstitial edema was believed to be the precursor of the interstitial pneumonitis. Clouston described a case of systemic lupus erythematosus in which the alveolar walls of the lungs presented a picture not unlike the appearance of the so-called wire loop lesions found in the kidneys. Others have called special attention to the acute arteritic changes of the pulmonary blood vessels.

ROENTGENOLOGY

The roentgen findings of systemic lupus erythematosus, with reference to the pleuropulmonary involvement, are in keeping with the pathological process. Although abnormal changes are encountered, they are not characteristic of the disease. However, the changes assume added importance if the nature of the systemic disease is known or suspected (Figure 29). If experience with other collagen diseases can serve as a guide, it is very likely that once the significance of the roentgenological changes is fully appreciated, the chest x-ray will also serve as an aid in the diagnosis of obscure disease. Tumults ascribes particular significance to patchy pleuratic areas in the basal portions of the lungs and the resulting elevation of the diaphragm. In the fifty-four autopsied cases, reported by Purnell and co-workers, focal or diffuse atelectasis was found in 44.3 per cent. A case is reported by Ellman and Cudkowitz of a young woman who became ill with an acute febrile disease characterized by cyanosis and dyspnea. A shadow at the right base was regarded as being due to a subphrenic abscess but at operation no pus was found. Later a diffuse opacity was seen at the right base as well as mottling at the left lower lobe. The left subphrenic space was then explored surgically and again no pus was found. Three months later an erythema appeared on the face and the diagnosis of lupus erythematosus was no longer in doubt.

Israel reported twenty-eight patients with established diagnosis of disseminated lupus erythematosus, in nine, confirmed at autopsy. Roentgen or pathologic evidence of pulmonary involvement was found in twenty of the twenty-two patients. Fifteen patients showed, on one or more admissions, clinical and roentgen evidence of pneumonia, in two, previously suspected pneumonias were found at autopsy. Two patients had pleurisy with large effusions and one patient had diffuse perivascular or vascular changes. Israel was able to differentiate three groups of cases with varying pulmonary patterns. One form was characterized by recurrent pneumonia, a second showed lesions simulating

tuberculosis, and a third had predominantly respiratory symptoms.

Bille, also Thorell, directed attention to the pleural and subpleural changes. In a study of five cases there were pleural changes noted in the chest x-rays consisting of pleural thickening, small effusions and subpleural changes in the adjacent parenchyma best demonstrated in oblique projections. The frequency of pleural involvement is brought out in the study of Purnell and co-workers. No less than two-thirds of the patients had pleural effusions. It was bilateral in 48.1 per cent and unilateral in 18.5 per cent. Unexplained pleural effusions, especially if bilateral, occurring in women in whom there may be reason to suspect a systemic disturbance, should bring to mind the possible presence of disseminated lupus erythematosus. Small pleural effusions are often associated with oblique or horizontal striations, the exact nature of which is problematic (Figure 30B).

In patients in whom the disease pursues a more chronic course, one may encounter chest x-ray findings in keeping with a diffuse interstitial fibrosis associated with small pleural effusions, very much like the changes seen in other collagen diseases. The following case illustrates the "classical" features of disseminated lupus erythematosus, including the pleuropulmonary changes.

Case 19 Female—Age 19

A white girl was admitted to the Morrisania City Hospital July 5, 1950 complaining of joint pains, weakness and loss of twenty-five pounds in weight. Her illness began three months previously with fever, enlarged glands and sore throat. The patient was admitted then to another hospital where the condition was diagnosed as glandular fever for which she was treated. Several weeks before entering the Morrisania City Hospital the patient developed a rash over the bridge of the nose. Physical examination revealed an acutely ill girl with marked limitation of motion of the back and extremities. At this time there was no erythema on the face. There was a fusiform swelling of the first proximal phalangeal joint and generalized lymphadenopathy. The spleen was palpable. Blood examinations showed leucopenia, anemia and L.E. cells. Chest x-rays did not show any significant abnormalities.

A diagnosis of disseminated lupus erythematosus was made.

The patient was placed on cortisone 100 mg daily and after one week's treatment there was some improvement. The temperature declined with diminution in the phalangeal swelling and increased motion of the joint. However at this time a butterfly erythema appeared on the face (Figure 30A, B and C). Cortisone was continued for six weeks but the joint pains soon recurred. The patient was then treated with ACTH. A week later the patient developed pain in the left chest and soon fluid

appeared in the pleural cavity. The aspirated specimen showed large numbers of eosinophils and mononuclear cells, no other abnormal cells. Corticosteroid treatment was resumed, 100 mg daily, but the chest pain persisted and was associated with fever and dyspnea.

Two months later the patient developed severe respiratory distress and signs of heart failure. The physical and x-ray examinations now revealed fluid in both pleural cavities as well as in the pericardium (Figure 30D). The presence of the latter was confirmed by needle aspiration which revealed blood.

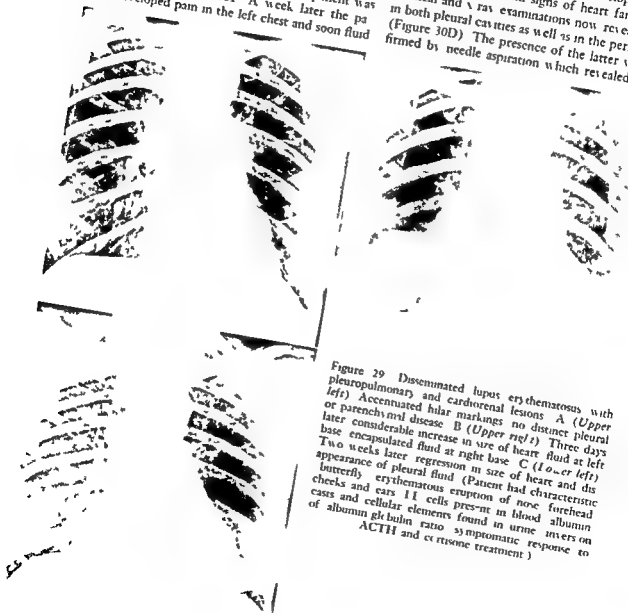


Figure 29 Disseminated lupus erythematosus with pleuropulmonary and cardiorenal lesions. A (Upper left) Accentuated hilar markings. B (Upper right) Three days later considerable increase in size of heart fluid at left base encapsulated fluid at right base. C (Lower left) Two weeks later regression in size of heart and disappearance of pleural fluid (Patient had characteristic butterfly erythematous eruption of nose, forehead, cheeks and ears. LE cells present in blood, uric acid casts and cellular elements found in urine. albumin of albumin globulin ratio symptomatic response to ACTH and cortisone treatment.)

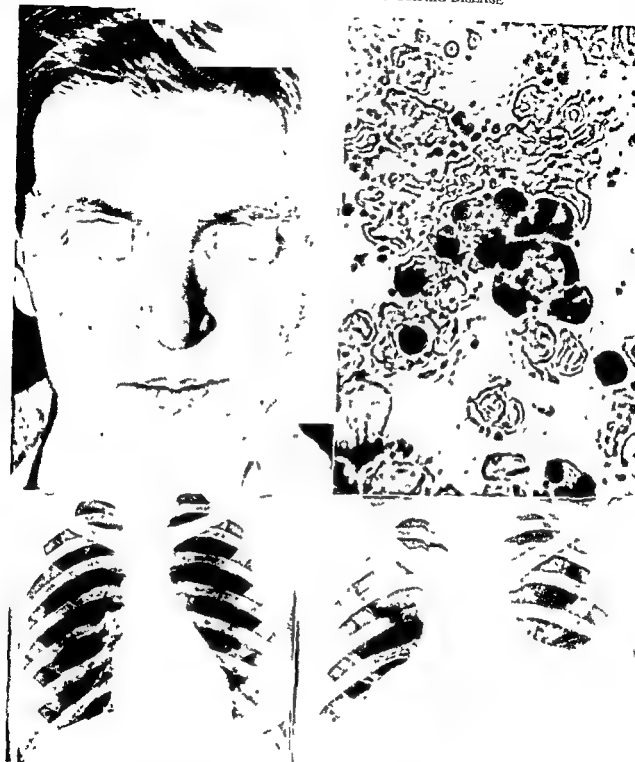


Figure 30 Case 19 Disseminated lupus erythematosus with pleuropulmonary and pericardial lesions A (Upper left) Characteristic butterfly rash on bridge of nose and cheeks B (Upper right) 'LE' cluster and polymorphonuclear cell containing masses of homogenous material C (Lower left) Chest x ray shows no abnormalities D (Lower right) Five months later, faint, round infiltration in right upper lobe, linear striations in right lower lung field, fluid in both pleural cavities, cardiac shadow enlarged with pericardial effusion (Autopsy revealed fibrinous, gelatinous exudate in both pleural cavities and in pericardial cavity, edema and congestion of lungs, glomerular lesions of kidney with suggestive 'wire-loop' appearance)

tinged serous fluid. In addition the chest x ray now revealed a soft round homogeneous density in the right upper lobe as well as linear streaks paralleling the small fissure. For a time the patient showed signs of improvement and she was treated at home with cortisone and periodic chest aspirations. Later the patient developed anasarca which was partially relieved with mercurhydriol. She was readmitted to the hospital. On July 19, 1951 the patient sustained a severe nasal hemorrhage and died.

Autopsy revealed marked fibrous adhesions within the thorax binding down the viscera. The lungs were covered by a thick gelatinous fibrinous

exudate which dipped between the lobes of both lungs. On cut section the lungs were markedly congested, firm and atelectatic. There was a frothy sanguinous exudate expressed from the cut surface. The fibrinous gelatinous exudate also covered the pericardium which was intimately attached to the heart. Exudate was present on the surface of the heart but the valves were normal. Microscopic examination revealed the pleural surface thickened by fibrin with minimal exudate, no eosinophils were seen. The lung parenchyma showed edema and congestion. The final diagnosis was disseminated lupus erythematosus with pericardial and pleuropulmonary involvement.

Mycosis Fungoides

Mycosis fungoides is a disease characterized by erythematous, eczematoid, urticarial or mixed lesions of the skin which gradually infiltrate and thicken the epidermis in time producing nodular ulcerative or fungating masses. As is often the case in dermatology, mycosis fungoides is a misnomer. The disease is neither a mycotic infection nor a fungating tumor, nor is it limited to the skin. Some investigators consider mycosis fungoides a tumor-like disease; others include the condition among the lymphoblastomas because the terminal picture may assume the features of Hodgkin's disease, lymphosarcoma or lymphatic leukemia. Bluefarb lists nine diverse opinions regarding the nosologic status of mycosis fungoides and adds a tenth, namely, that it is a disease of the reticuloendothelial system, an opinion shared by many others. All agree that the skin lesions are simply an outward expression of a generalized disease. Bermin, in a review of sixty cases reported in the literature from 1928 to 1938, found that of eighteen cases examined at autopsy, sixteen had involvement of internal organs and one probable involvement. The organs most often affected are the spleen, liver and lungs.

Kuznitzky, in 1916, was among the first to direct attention to the pulmonary lesions in mycosis fungoides. The three cases he described showed roentgenologically prominent hilar markings and infiltrations of the adjacent lung parenchyma. In 1940, Werth reviewed the pulmonary findings of mycosis fungoides and found reports

of thirty-one cases which contained reference to the lungs, but very few of these included chest x rays. The paucity of adequate descriptions of the pulmonary manifestations is undoubtedly due to the failure of most dermatologists to have chest x rays taken of patients with skin diseases. This is forcefully illustrated in a recent study of Bluefarb and Steinberg who reported no less than four cases of mycosis fungoides in which round infiltrates were demonstrable in the lungs roentgenologically. In three the nature of the pulmonary involvement was verified at autopsy, the fourth showed clearing of the infiltrations following nitrogen mustard and radioactive phosphorus. The following case illustrates the pulmonary findings in mycosis fungoides.

Case 20. Male—Age 59

A white male was admitted to the Montefiore Hospital with a skin disease of three years' duration. The disease had made its initial appearance on the right leg. The lesions soon increased in number, became fungating and covered almost the entire body (Figure 31A). Biopsy of skin tissue revealed papillary protrusions extending for some distance into the corium where large numbers of lymphocytes and plasma cells were arranged about the small vessels and about the hair follicles. The cells were in edematous, loose fibrillar connective tissue. The picture was considered in keeping with early infiltrative mycosis fungoides. Except for the skin lesions, no other significant abnormalities were found. A chest x ray at this time revealed a circumscribed infiltration in the right upper lobe and ac-



Figure 31 Case 20 Mycosis fungoides with pulmonary lesions A (Left) Nodular and ulcerative lesions of skin of trunk, arms and legs (Biopsy of skin revealed changes consistent with mycosis fungoides) B (Right) Chest x ray reveals a large collection of fluid in the right pleural cavity scattered rounded densities in both lungs (At autopsy lungs revealed numerous small well demarcated nodules also involvement of regional lymph nodes vertebrae liver spleen kidneys and adrenals)

centuation of the bronchovascular markings in both lungs

A year after admission the patient developed fluid in the right chest which was aspirated and found to be a clear exudate containing large and small mononuclear cells but no bacteria. The chest x ray now revealed in addition to the collection of fluid scattered rounded infiltrations in both lungs (Figure 31B). In spite of radiotherapy the course of the disease was steadily downhill and the patient died twenty one months after admission. Autopsy revealed fluid in both pleural cavities. The

lungs contained numerous small well demarcated firm nodules some with reddish centers the intervening tissue was emphysematous. Histologic examination revealed tumor nests of polyhedral cells in the pleura as well as in the lungs. The skin showed similar masses of tumor cells invading and replacing the normal connective tissue bundles of the corium. The cells were irregular polygonal with large hyperchromatic nuclei. They assumed a definite perivascular arrangement. In addition there was involvement of the regional lymph nodes vertebrae liver spleen kidneys and adrenals.

Neurocutaneous Diseases

There are a number of syndromes grouped under this heading which have long been favorite topics of discussion by dermatologists and neurologists. Of late internists have become aware of these intriguing diseases because they may be associated with systemic manifestations including Addison's disease, acromegaly, myxedema and other disturbances. The several conditions include developmental defects, neoplastic

formations as well as endocrine gland involvements. As might be expected, mental deficiency and epilepsy are frequent. With increasing use of routine chest x rays, physicians interested in chest diseases have occasion to encounter pulmonary lesions associated with these neurocutaneous syndromes.

The neurocutaneous group of diseases include a variety of disorders involving a mixture of

structures and tissues. They are all probably closely allied, some manifesting themselves externally, others internally. Heublen and co-workers distinguish four major neurocutaneous entities: (A) Tuberous Sclerosis, (B) Von Recklinghausen's Neurofibromatosis, (C) Angioma and (D) Von Hippel-Landau's Disease. To date, only the first two have been found associated with intrathoracic manifestations.

A case reported by Budenz had neurofibromatosis of the skin, tuberous sclerosis and caseous lesions in the calvarium, ribs, humeri and femora, multiple polyposis of the colon and a mediastinal tumor. Two crises of Von Recklinghausen's disease with bone manifestations were reported by Uhlmann and Grossman in one of which the chest x-ray revealed a large cervical mass involving the upper mediastinum with decalcification, atrophy and deformity of the adjacent cervical vertebrae. Other features in the cases included cystic changes in the mandible, gigantism and bowing of the tibia associated with elephantiasis of the lower extremity and osteoporosis. A number of other cases have been described featuring bizarre combinations of organ and tissue involvements.

TUBEROUS SCLEROSIS

This is a rare condition characterized by the following mental deficiency, epileptiform seizures, an acneiform rash of butterfly distribution on the face (adenoma sebaceum or Pringle's disease) and tumors which may affect various parts of the body, especially the brain, kidneys and eyes. Periungual and subungual fibromas as well as skeletal changes are often encountered. Pathologically the disease is featured by potato-like sclerotic patches involving chiefly the surfaces and ventricles of the brain,—hence the name, tuberous sclerosis. Calcified areas in the calvarium and within the brain substances may be demonstrable roentgenologically.

In 1938 Berg published an example of cystic disease of the lungs and several years later, in association with Veylens and Zachrisson reported three crises of tuberous sclerosis showing peculiar cystic changes in the lungs. Particularly interest-

ing was the discovery of the disease in two sisters, both of whom had adenoma sebaceum of the face and ungual fibromas of some of the fingers and toes. A brother of these two sisters also had adenoma sebaceum and calcifications of the brain. A familial occurrence of the disease has been noted by others. The chest x-ray of one of the sisters who later died of asphyxia and in whom it was possible to verify the diagnosis at autopsy, revealed "a well-defined net-like pattern symmetrically spread over both lung fields, caused by closely situated, round translucencies, some so small as to be hardly visible, others varying in size up to that of hazel-nuts. The translucencies were separated by relatively narrow, thin septa." The pathologic changes were in keeping with the roentgen findings. The lung parenchyma was the seat of innumerable large and small cysts. On histologic examination the involved lung was found to consist of connective tissue, blood vessels and, quite strikingly, smooth muscle elements having an unmistakable character of tumor tissue. Tumorous changes were also found in the brain and kidneys. The films and lung specimens of the patients reported by Berg, Veylens and Zachrisson, also by Ackermann, also by Silverstein and Mitchell are almost identical. The cystic changes in the lungs resemble roentgenologically those seen in histiocytosis and in cystic lungs described in Chapter 3.

In a comprehensive review of the pulmonary manifestations of tuberous sclerosis and its relationship to other forms of the disease, Dawson described four cases of pulmonary tuberous sclerosis and analyzed the findings of nine reported by others. The chief features were the predominance of the disease among women. The pulmonary symptoms were characterized by progressive shortness of breath, recurrent pneumothorax, occasional hemoptysis and an absence or late development of concomitant infection. The roentgen findings consisted of diffuse miliary or small cystic changes. Death followed about five years after the onset of symptoms due to asphyxiation from lung destruction or as a result of a spontaneous pneumothorax or right heart failure. The pathological changes seen in lung biopsy specimens from two of the cases studied by Dawson



Figure 32 Case 21 Tuberous sclerosis with pulmonary lesions. A (Left) Symmetric eruption on the nose and adjacent cheek and to a lesser extent chin and forehead. B (Right) Warty swellings of subungual fibromas with ridging of the nails (Continued on next page)

corresponded with previous descriptions of the disease. The changes consisted of profuse overgrowth of connective tissue including smooth muscle and blood vessels leading to the formation of numerous small cysts. The following is an abstract of the history and lung biopsy findings of one of the cases of tuberous sclerosis reported by Dawson:

Case 21 Female—Age 30

During a period of three years the patient had recurrent seizures of chest pain and dyspnea. At the time of the recognition of her disease in the course of a routine chest x ray the patient had the seventh such episode. The chest x ray at this time revealed a partial left sided pneumothorax with a small pleural effusion. The past history revealed that at the age of five years the patient developed a facial eruption which became more conspicuous in the subsequent five years. From the

age of eight to ten years the patient suffered from recurrent Jacksonian convulsions but she never lost consciousness.

Physical examination revealed a symmetric eruption of the skin of the nose and adjacent cheek and to a lesser extent the chin and forehead. In the left lumbar region there was a small patch of peau d'agrine. The nails of three fingers and eight toes were deformed by warty swellings arising from the lateral edges of the nail base (Figures 32A and B). No abnormalities were found elsewhere except for a moderate enlargement of the kidneys which were deformed by several rounded lumps. Examination of the urine was negative. Additional

Edwards

The left fibula showed subperosteal thickening and an oval translucency at its lower end. Several of the phalanges showed subperosteal nodes. Excretion urography confirmed the presence of renal



Figure 37C. Chest x-ray (enlarged view of portion of lung) shows several small groups of cysts and generalized reticulation. (Continued on next page)

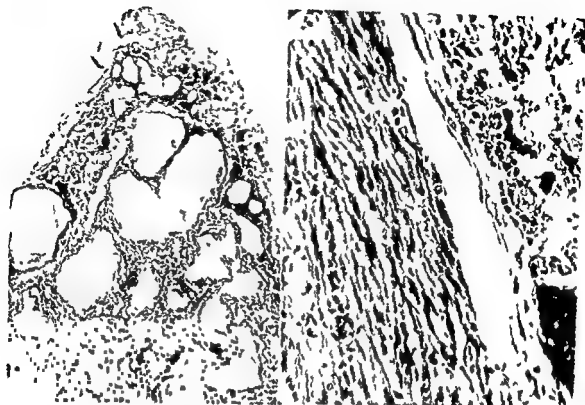


Figure 32D (Left) Biopsy specimen from right lung shows cyst like spaces. E (Right) Biopsy specimen from left lung shows a band of smooth muscle fibers to the right is a strand of fibroblasts and a collection of macrophages loaded with iron pigment (From Dawson, *Quint J Med*, 23:113, 1934)

enlargement and showed deformity of the lower calices on the right side. The patient returned home and went to work. She soon developed another spontaneous pneumothorax on the left side and after an interval of nine months in eighth seizure of chest pain and dyspnea this time the pain on the right side.

On readmission to the hospital the patient showed a right sided pneumothorax with complete collapse of the lung. The lung did not reexpand because of the presence of a bronchopleural fistula. A thoracotomy was done. The lung was found deeply colored dark blue, the surface covered by milium nodules probably caused by subpleural blebs. A biopsy specimen was taken. The pleural layers were painted with 5 per cent silver nitrate solution and shortly thereafter the lung reexpanded. A month later a spontaneous pneumothorax recurred on the left side. The chest was opened and the appearance of the lung was the same as that seen previously on the right side. A biopsy specimen was removed. Both pleural layers were painted with 5 per cent silver nitrate solution and the lung reexpanded fully within five days.

Histological examination of the right lung biopsy showed condensed lung tissue with cyst like spaces, several incompletely lined by cuboidal epithelium (Figure 32D). The left lung biopsy specimen presented a spongy appearance due to small spherical cysts. These were lined by low columnar or cuboidal epithelium. In addition there were completely solid areas composed of cuboidal cells together with small bands of smooth muscle fibers and fibroblasts (Figure 32E). In the sections of the left and right lungs there were large numbers of iron pigment containing macrophages lying free in the cysts and alveoli as well as within the lung parenchyma probably due to hemorrhages from the vascular walls of the lung cysts. A finger biopsy specimen showed squamous cell papilloma.

VON RECKLINGHAUSEN'S DISEASE (Neurofibromatosis)

This disease, described by its discoverer in 1882, is most often seen in the form of multiple fibromas and neuromas in the skin with or without cutaneous pigmentation. Neurofibromas

within the thoracic cavity may be encountered as part of a generalized process affecting the skin, sensory, skeletal and other organs. Heubelen and co-workers emphasize the striking similarity between tuberous sclerosis and Von Recklinghausen's neurofibromatosis. These authors quote Zimmerman to the effect that tuberous sclerosis is actually a central form of Von Recklinghausen's disease while Von Recklinghausen's disease is a form of peripheral tuberous sclerosis.

Intrathoracic neurofibromatosis have been found in association with intercostal, the vagus and sympathetic nerves. The lungs themselves are rarely involved even when the disease is widespread in other organs. The reader is referred to a complete review of the subject in a study by Kienbock and Rosler. In the thorax, the favorite location of these tumors is in the upper chest, retropleurally, adjacent to the spine. The tumors are usually discovered incidentally in routine chest x-rays (Figures 33A and B). During World War II a sizable number were detected in this manner among inductees. A tentative diagnosis of neurogenic tumor is made because of the location of the tumors in the posterior portion of the chest adjacent to the spine, a definitive diagnosis can be established only after surgical exploration. Approximately 10 per cent of intrathoracic neurogenic tumors undergo malignant changes. The tumors are of special interest to thoracic surgeons and quite a number have been removed successfully. The tumor may have an hour glass extension in the spinal cord. The lung parenchyma is rarely involved. Kent and his co-workers collected seventy-eight cases of primary intrathoracic neurogenic tumors reported in the literature with an incidence of 15.3 per cent of malignancy.

An unusual instance of solitary benign neurofibroma within the substance of the lung which was removed surgically was reported by Touroff and Sapin in 1949. A search of the literature by these authors revealed another case, published by Birtlett and Adams in 1946, of a solitary neurogenic tumor attached to the left main bronchus. The tumor a neuroma was removed by pneumonectomy. The third case, cited by Touroff and Sapin, was the following instance

of multiple neurofibromatosis limited to the lungs, described by Aronson and myself in 1940.

Case 22 Female—Age 57

A Negro housewife was admitted to the Morrisania City Hospital on September 12, 1934. Her chief complaints were asthma like seizures precipitated by upper respiratory infections. The present episode lasted about a week and was associated with pain in the left chest, dyspnea, cough and bloody expectoration. Past history revealed an attack of right sided pleurisy following influenza in 1917. She had an abdominal hysterectomy, salpingo-oophorectomy and appendicectomy in 1916. For about ten years, the patient had known that she had diabetes.

The patient did not appear acutely ill. The temperature and pulse were not elevated. The heart was moderately enlarged, blood pressure 140/90. Blood Wassermann was 3 plus. Blood examination showed moderate anemia and slight leukocytosis. The urine contained 7 plus glucose, no acetone and a few pus cells. A chest x-ray disclosed a number of sharply circumscribed homogeneous densities of varying size, irregularly distributed in both lung fields. The appearance of the nodules was in keeping with a metastatic neoplasm. Examination of the gastrointestinal, urogenital and skeletal systems failed to reveal a possible primary site. After an uneventful stay of six weeks in the hospital the diabetes being controlled by diet, the patient was discharged. The final diagnoses were diabetes mellitus, syphilis, essential hypertension, pulmonary metastases from an unknown site.

Four years later the patient was readmitted to the Morrisania City Hospital with fever and chills of four days duration. There was a moderate elevation of temperature but otherwise no significant changes from those noted on the first admission. A chest x-ray revealed the round densities in both lungs identical in size and distribution with those noted four years previously. Metastatic carcinoma seemed hardly likely and a careful search was made for an underlying cause. A mild cystitis and pyelitis were the only abnormalities found. Shortly after admission the patient developed increased cough, pain in the chest and bloody expectoration. A needle was inserted into the right lung at the angle of the scapula and about 10 cc of greenish, moderately thick pus aspirated without difficulty. Culture of the pus showed staphylococcus albus.

A chest x-ray taken eight days after the thoracic

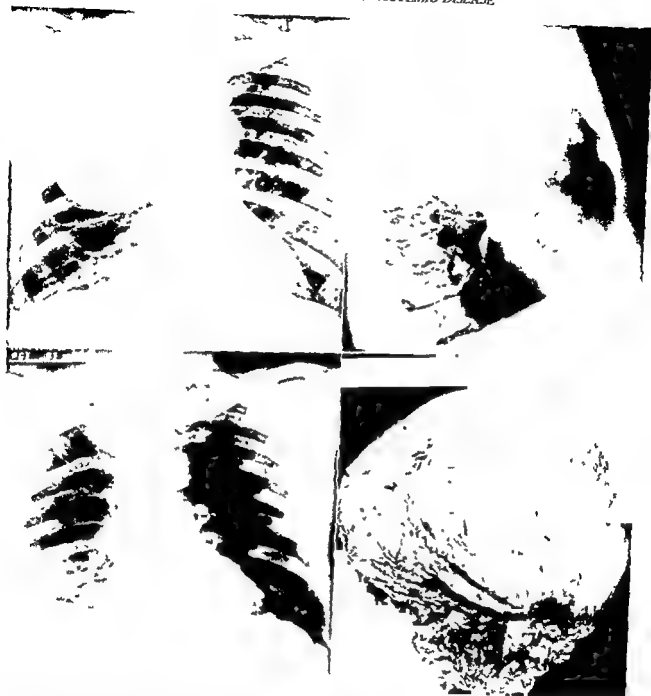


Figure 33 Intrathoracic neurogenic tumor (discovered accidentally on routine fluoroscopy, no symptoms referable to chest) A and B (Upper left and right) Large, oval, homogeneous density occupying upper half of right chest calcification of lower border, thickened horizontal fissure, osteoarthritis of thoracic spine C (Lower left) One month after excision of tumor, right lung completely reexpanded, interlobar fissure drawn upward pleuritic reaction at right base D (Lower right) Resected specimen (At operation a large, spherical tumor was found attached by a pedicle to the paravertebral gutter in the region of the second intercostal nerve Upon removal of the mass, the lung expanded completely and filled the hemithorax The tumor, a soft cyst weighing 1050 grams was filled with slightly blood tinged serous fluid, cyst capsule was thick and contained many foci of calcification Microscopic examination showed histologic features of a neurofibroma)

centesis revealed a collection of air surmounting a fluid level at the site of the lung puncture (Figure 34A). Apparently a broken down mass in the lung had been partly evacuated. The patient's course continued progressively downhill with high fever and repeated hemoptyses. The dyspnea became uncontrollable. The patient began to complain of headache and stiffness of the neck. Spinal puncture revealed cloudy fluid containing about 2,000 leukocytes per cc. No organisms could be cultured. The patient died December 27, 1938 with symptoms of basilar meningitis.

At autopsy aside from a markedly purulent meningitis at the base of the brain the lungs were the only organs to reveal abnormalities. The pleural cavities contained no fluid. The left pleural cavity had a few small adhesions at the apex but was otherwise free. The right lung had a moderate number of adhesions over the posterolateral aspects. The surface of both organs were numerous projections of tissue varying in size from 0.5 to 3 cm. These projections flat with the lung surface and narrow pedicles by which they were attached to the lungs. On section they appeared to be yellowish and somewhat firmer than fat tissue. Sections of both lungs revealed numerous nodules within the parenchyma of the same type as found on the surface of the lungs (Figure 34B). In the right lung one of the nodules about 3 cm in diameter was found to contain a cavity filled with purulent material.

A careful histological study was made of the structure of these nodules by Dr. G. A. Jarvis of the New York State Psychiatric Institute and Hospital. It was Dr. Jarvis' opinion that the tumor was a neurofibroma. The typical association of elongated fibers, left little doubt as to the diagnosis. The absence of nerve fibers and the arrangement of cells and fibers indicated that the tumor belonged to the type A neurofibroma of Antoni. According to Penfield's classification the tumor could be classified as a perineural fibroblastoma.

Before concluding the section on the pulmonary manifestations of certain neurocutaneous diseases it may be in order to refer briefly to the occasional association of bronchiogenic carcinoma and myasthenia gravis. Anderson and co-workers published the case of a man of forty

seven who developed progressive muscle weakness, transient diplopia, difficulty in swallowing and other evidence of myasthenia gravis. The diagnosis being supported by symptomatic improvement after oral treatment with neostigmine. The chest x-ray revealed enlargement of the right upper lobe with enlarged lymph nodes. A bronchial biopsy showed carcinoma. On another occasion the same author encountered a comparable instance in which a peripheral neuropathy, similar to myasthenia gravis disappeared after the removal of a bronchial neoplasm. Following the appearance of Anderson's report Mackenzie also Shafer cited similar instances of myasthenia gravis associated with bronchiogenic carcinoma. In one case the diagnosis was proved by pneumonectomy, in the other at autopsy.

It may be pertinent to mention the frequent finding of abnormalities of the thymus in patients with myasthenia gravis. Black and co-workers estimate that the combination occurs in approximately half of the patients examined at autopsy. On the basis of this apparent relationship Black and others have utilized total thymectomy in the treatment of myasthenia gravis. Ross reported the results of thymectomy in 100 patients with myasthenia gravis due to simple hyperplasia of the thymus. Various degrees of improvement as judged by the reduction in daily neostigmine requirement after operation were obtained in 87 per cent. The results of thymectomy depend to a large extent on the duration of the disease preceding the operation, the shorter the period the better the chances of improvement.

Although not directly related to the subject under discussion it might also be mentioned that bronchiogenic carcinoma may be associated with peripheral neuritis. In the opinion of Lennor and Pritchard such an association is probably not a matter of coincidence. Since the incidence of bronchiogenic carcinoma is rising precipitously chiefly in elderly persons any possible relationship of muscular and neurological abnormalities will have to be studied with particular care to exclude the factor of chance association.

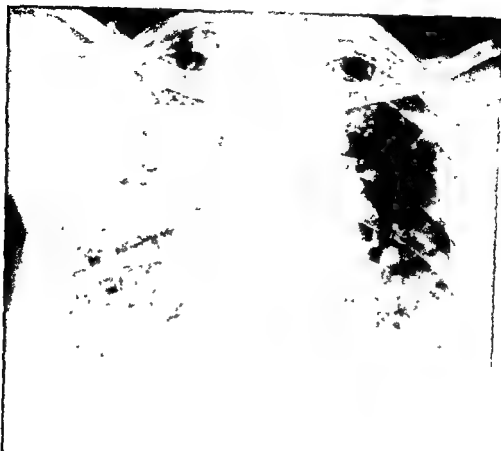


Figure 34A (See legend on opposite page)

Bibliography

ALLERGIC DERMATITIS

- FALK M S, and NEWCOMER V D: Loeffler's Syndrome Occurrence in Two Patients Treated with Penicillin in Oil and Wax. *J A M A*, 141:21, 1949
- FROSTHER, N.: On Lung Changes in Acute General Dermatitis. *Acta radiol*, 29:493, 1948
- KIRBY-SMITH, J L, DOVE, W E and WHITE, G F: Creeping Eruption. *Arch Dermat & Syph*, 13:137, 1926
- WRIGHT, D O, and GOLD E M: Loeffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis). *Arch Int Med*, 78:303, 1946

ERYTHEMA MULTIFORME

- ACOSTAS, W N, REEVES N, SHANAS, E D, and WIDEN STRICKER, V P: Erythema Multiforme Bullosum (Stevens Johnson Syndrome). *New England J Med*, 246:216, 1952
- ANDERSEN, W T: Eruptive Fever. Correspondence. *Arch Int Med*, 80:413, 1947
- ASHBY, D W, and LAZAR T: Erythema Multiforme Exudativum Major (Stevens-Johnson Syndrome). *Lancet*, 1:1091, 1951
- Commission on Acute Respiratory Diseases: Association of Pneumonia with Erythema Multiforme Exudativum. *Arch Int Med*, 79:687, 1946
- COSTELLO M J: Erythema Multiforme Exudativum (Erythema Bullosum Majus—Platonic Type). *J Invest Dermat*, 9:127, 1947
- FINLAND, M, JOLLIFFE, L S, and PARKER, F, Jr: Pneumonia and Erythema Multiforme Exudativum. *Am J Med*, 4:473, 1948
- KELL, H: Erythema Multiforme Exudativum (Hebra). A Clinical Entity Associated with Systemic Features. *Ann Int Med*, 14:449, 1940
- MARSHALL, J D: Discussion re Clinical Meeting of the Kingston Garrison Medical Society. *J Canad M Serv*, 1:471, 1949
- MICHELSON, H F: The Boundaries of Dermatology. *Arch Dermat & Syph*, 65:1, 1952
- OSLER, W: On the Visceral Manifestations of the Erythema Group of Skin Diseases. *Tr A Am Physicians*, 18:1599, 1903
- SILVIA, O: Erythema Multiforme Exudativum and Pneumonia. *Acta M Scand*, 135:34, 1949
- SOLA, E N: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balinitis. *Arch Int Med*, 79:475, 1947.



Figure 34 Case 22 Neurofibromatosis of the lungs A (Opposite page) Scattered, round densities of uneven size in both lungs (Fluid level in mass in right upper lobe after needle aspiration) B (Above) Lung section shows multiple round nodules (Microscopic examination of nodules showed fibres and cells in palisade arrangement also elongated nuclei with delicate fibres and small cysts lined by endothelium) (From Rubin and Aronson *Am Rev. Tuberc.* 41:801 1940)

- STANSON J. H. and WARNER W. P. Mucosal Respiratory Syndrome *J. Canad. M. A.* 53:45 1945
- STEVENS A. M. and JOHNSON I. C. A New Eruptive Fever Associated with Stomatitis and Epithelitis Report of Two Cases in Children *Am. J. Dis. Child.* 24:676 1922
- FULLERTON P. A. The Clinical Course of Systemic Lupus Erythematosus *J. I. M. I.* 116:997 1954
- VON HERRA I. *Diseases of the Skin* translated and edited by C. H. Jaeger. New Sydenham Society London 1866
- WENDE H. S. and STEVENS A. M. Stevens Johnson Syndrome A Variation of Erythema Multiforme Exudativum (Hebra) A Report of Two Cases *Ann. Int. Med.* 14:194 1941
- YARIS H. BRUCE C. ANDERSON W., LEVY F., and MITCHELL I. Erythema Multiforme Bullsum (Stevens Johnson) Treated with LORSONE *Can. Proc. Child.* 11:14 1941
- ERYTHEMA NODOSUM**
- BRIDMAN H. Erythema Nodosum A Survey of Some Recent Literature *Am. J. M. Sc.* 22:415 1951
- CRAWLEY J. I. Erythema Nodosum As Initial Manifestation of Rocks Sarcoma *Brit. M. J.* 2:1162 1950
- DESSER I. and HERNON R. Erythema Nodum with Bilateral Hilar Gland Enlargement *Brit. M. J.* 2:1078 1952
- FAVIER C. B. and SOSSMAN M. C. Erythema Nodosum *Arch. Int. Med.* 40:415 1947
- HOLMES C. H. OLSEN A. M. and GORDON C. A. Bilateral Hilar Adenopathy Its Significance and Management *Ann. Int. Med.* 43:383 1955
- JOHNSON C. C., HANSON N. L., and COON C. A. Erythema Nodum The Possible Significance of Associated Pulmonary Hilar Adenopathy *Ann. Int. Med.* 34:983 1951
- KERLEY P. The Etiology of Erythema Nodosum *Brit. J. Radiol.* 16:199 1943
- LINCOLN, I. M., ALTMAN J. and BASTY H. Erythema Nodum in Children *J. Pediatr.* 25:111 1944
- LOUGHEE S. Erythema Nodosum Studies on Etiology and Pathogenesis *Acta Med. Scandinavica* 124:1 1946, Supp. 174
- LOUGHEE S. and WATKINS, F. On the Histopathology of Erythema Nodosum *Acta Dermatovenereol.* 29:1 1949
- MURPHY J. H. Erythema Nodosum *Brit. J. Radiol.* 22:175 1949

- USTVEDT H J Further Investigations Concerning the Relation Between Erythema Nodosum and Tuberculosis *Tubercle* 28 747 1947
- WALLGREN A Postprimary Erythema Nodosum Tuberculosis *Acta tuberc scandinav*, 91 1935

DISSEMINATED LUPUS ERYTHEMATOSUS

- BAEHR G and POLLACK A D Disseminated Lupus Erythematosus and Diffuse Scleroderma *J A M A*, 134 1169 1947
- BAGGENSTOSS A H Visceral Lesions in Disseminated Lupus Erythematosus *Proc Staff Meet Mayo Clinic* 27 417 1952
- BEV ASHER S Recurrent Acute Lupus Erythematosus Disseminatus Report of a Case Which Has Survived Twenty Three Years After the Onset of Systemic Manifestations *Ann Int Med* 34 743 1951
- CLAYTON H C JR Acute Lupus Erythematosus Disseminatus *Ann Int Med* 19 843 1943
- COHEN A K Disseminated Lupus Erythematosus A Clinico-Pathological Review of Seven Cases *Australian Ann Med* 3 64 1954
- DU BOIS E L The Effect of the L E Cell Test on the Clinical Picture of Systemic Lupus Erythematosus *Ann Int Med* 38 1765 1953
- ELLMAN P and CUDKOWICZ L Pulmonary Manifestations in the Diffuse Collagen Diseases *Thorax* 9 46 1954
- GINZLER A M and FOX T T Disseminated Lupus Erythematosus A Cutaneous Manifestation of a Systemic Disease (Libman Sacks) *Arch Int Med* 65 76 1940
- GRIFFITH E C and VURAL I L Acute and Subacute Disseminated Lupus Erythematosus A Correlation of Clinical and Postmortem Findings in Eighteen Cases *Circulation* 3 497 1951
- HARGRAVES M M, RICHMOND H and MORTON R Presentation of Two Bone Marrow Elements The "Tart Cell" and the L E Cell *Proc Staff Meet Mayo Clinic* 23 75 1948
- HASERICK J R Blood Factor in Acute Disseminated Lupus Erythematosus The L E Test *New York State J Med* 50 7445 1950
- HASERICK J R and SLYDBERG R D Bone Marrow as Diagnostic Aid in Acute Disseminated Lupus Erythematosus Report on Hargraves L E Cell *J Invest Dermatol* 11 209 1948
- HUGHREYS E M The Cardiac Lesions of Acute Disseminated Lupus Erythematosus *Ann Int Med* 28 17 1948
- ISRAEL H L The Pulmonary Manifestations of Disseminated Lupus Erythematosus *Am J M Sc* 226 387 1953
- JADASSOHN J Lupus Erythematosus in Virchow's *Handbuch der Hautkrankheiten* Vienna A Holder 1904 p 798 quoted by KEIL, H Conception of Lupus Erythematosus and its Morphologic Variants
- JESSAR R A, LAMONT HAYES R W and RAGAN C Natural History of Lupus Erythematosus Disseminatus. *Ann Int Med* 35 17 1953
- KAPONI M Neue Beiträge zur Kenntnis des Lupus erythematosus *Arch Dermat Syph*, 4 36 1877
- KEIL, H Conception of Lupus Erythematosus and its Morphologic Variants *Arch Dermat & Syph* 36 779 1937
- KEIL, H Relationship Between Lupus Erythematosus and Tuberculosis A Critical Review Based on Observations at Necropsy *Arch Dermat & Syph*, 28 765 1933
- KLEMPERER, P The Pathogenesis of Lupus Erythematosus and Allied Conditions *Ann Int Med*, 28 1 1948
- KLEMPERER P, GLEFF B, LESS S L, LELCHTENBERGER C, and POLLISTER A W Cytochemical Changes of Acute Lupus Erythematosus *Arch Pathol*, 49 503 1950
- KLEMPERER P, POLLACK, A D, and BAEHR G Pathology of Disseminated Lupus Erythematosus *Arch Pathol*, 57 569 1941
- LEE, S L, MICHAEL, M R and VURAL, I L The L E (Lupus Erythematosus) Cell *Clinical and Chemical Studies Am J Med* 10 446 1951
- MICHAELSON H C The Boundaries of Dermatology *Arch Dermat & Syph* 65 1 19 2
- MONTGOMERY H Disseminated Lupus Erythematosus *Arch Dermat & Syph*, 60 36 1949
- PALL, A M Occurrence of the L E Phenomenon in a Patient with a Severe Penicillin Reaction *New England J Med*, 257 178 1955
- PERNELL D C, BAGGENSTOSS A H, and OLSEN A M Pulmonary Lesions in Disseminated Lupus Erythematosus *Ann Int Med* 47 614 1955
- RAKOS H L and TAYLOR J S Acute Disseminated Lupus Erythematosus *Arch Int Med* 70 88 1941
- REIFENSTEIN E C, REIFENSTEIN E C JR, and REIFENSTEIN G H A Variable Symptom Complex of Undetermined Etiology With Fatal Termination *Arch Int Med* 63 553 1939
- ROBB, R J and BOND W H Some Supravital Observations on the L E Phenomenon *Am J Med* 17 477 1952
- SNICKLEY J M Systemic Involvement in Disseminated Lupus Erythematosus *Proc Staff Meet Mayo Clinic* 33 680 1940
- THORELL I Pulmonary Changes in Cases of Disseminated Lupus Erythematosus *Acta radiol*, 37 8 1952
- TELLER P A The Clinical Course of Systemic Lupus Erythematosus *J A M A*, 136 947 1934
- WALSHE J M, and ZIMMERMAN H J The Demonstration of the L E Phenomenon in Patients with Penicillin Hypersensitivity *Blood* 8 65 1953

MYCOSIS FUNGOIDES

- BERMAN L Pathologic Nature of Mycosis Fungoides *Arch Pathol* 29 530 1940
- BLUFARB S M Is Mycosis Fungoides an Entity? *Arch Dermat & Syph*, 71 793 1955
- BLUFARB S M, and STEINBERG, H S Pulmonary Manifestations of Mycosis Fungoides *Ann Int Med* 36 625 1957
- KALZITZKY F Über Lungenbefunde bei Mycosis fungoides und ihre Bedeutung *Arch Dermat & Syph* 173 453 1916
- POST C F and LINCOLN C S Mycosis Fungoides *J Invest Dermatol*, 10 135 1948
- VIEFA J O, and CRAVER L F Intrathoracic Manifestations of the Lymphomatoid Diseases *Radiology* 37 138 1941
- WERTH J Über Lungenröntgenbefunde bei Mycosis fungoides *Arch Dermat & Syph*, 181 799 1940

DISASES OF THE SKIN AND MUCOUS MEMBRANES

133

- ACKERMAN A J Pulmonary and Osseous Manifestations of Tuberculous Sclerosis with Some Remarks on Their Pathogenesis *Am J Roentgenol*, 51 315 1944
- ANDERSON H J CHURCHILL DAINSON H C, and RICHARDSON A T Bronchial Neoplasm with Myasthenia *Lancet* 2 1291 1953
- ARRETT J P and ADAMS W E Solitary Primary Neurogenic Tumor of the Lung *J Thoracic Surg*, 15 351 1946
- CHURCHILL DAINSON H C and ZACHARSON C G Cystic Lungs of Rare Origin—Tuberculous Sclerosis *Acta radiol*, 22 475 1941
- BLAUZAC A HARVEY A M, FORD F R and LINTHICUM J L, Jr The Treatment of Myasthenia Gravis by Removal of the Thymus Gland *J A M A* 117 1529 1941
- BOEDEN G C Tuberculous Sclerosis A Neurocutaneous Syndrome *Radiology* 55 522 1950
- DAINSON J Pulmonary Tuberculous Sclerosis And Its Relationship to Other Forms of the Disease *Quart J Med* 53 113 1954
- HECHT G W PENDERGRASS E P and MURPHY B P Roentgenographic Findings in Neurocutaneous Syndromes *Radiology* 55 701 1940
- KENT J N, BLAIR B A and GRAY A B, and GRAY A B Intrathoracic Neurogenic Tumors *J Thoracic Surg* 13 116, 1944
- KREIBER R and ROSLER H Neurofibromatose Fortschr Geb Röntgenstrahlen 47-9 1952
- LENNY B and PUGH S The Association of Bronchial Carcinoma and Peripheral Neuritis *Quart J Med*, 19 97 1950
- LENNY O L Recklinghausen's Disease Its Relation to the Endocrine System *Arch Dermat & Syph*, 4 103 1951
- LENNY H Myasthenia Gravis *Am J Med* 9 691, 1950
- MCKENZIE J Bronchial Neoplasm with Myasthenia *Lancet* 1 109 1954
- ROBINSON T A Case of Diffuse Myomatosis and Cyst Formation in the Lung *Acta Radiol* 23 138 1947
- ROBINSON T Thymectomy in the Treatment of Myasthenia Gravis *Lancet* 1 785 1952
- ROBINSON T and ANDERSON W Primary Neurofibroma of the Lung *Am Rev Tuberc*, 41-801 1940
- SAMUELS F Tuberculous Sclerosis with Changes in Lung and Fones *Acta radiol* 23 373 1947
- SILVERMAN J Bronchial Neoplasm with Myasthenia *Lancet* 1 109 1954
- SILVERSTEIN C M and MURPHY G L Tuberculous Sclerosis *Am J Med*, 16 764 1954
- TOLROFF A S W, and SAPIR S O Solitary Intrathoracic Neurofibroma *Surgery* 26 787 1949
- LENNY F, and GROSSMAN, A Von Recklinghausen's Neurofibromatosis with Bone Manifestations *Ann Int Med* 14 225 1940
- LENNY G Specific Pulmonary Alterations in Tuberculous Sclerosis *Acta path et microbiol scandinav*, 18 317 1941
- VON RECKLINGHAUSEN F Leber der multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen Berlin, Hirschwald 1882

Diseases of the Skin and Mucous Membranes (Continued)

Diseases of the Skin and Malignant Tumors

IN AN INSTRUCTIVE exhibit Curth collected a variety of non neoplastic dermatoses which may be associated with malignant internal tumors. Of particular interest from the view point of the present discussion are the skin diseases which may be found in association with intrathoracic tumors.

In reviewing the various dermatoses which may be associated with neoplastic disease one is struck by the fact that collagen diseases appear to be favored. Since collagen is the major component of the integument such an association is to be expected. However the relationship is at times so striking that other factors are undoubtedly also involved. Lansbury commented on the association of neoplasms including bronchiogenic carcinoma and rheumatoid arthritis, dermatomyositis and disseminated lupus erythematosus. As will be indicated shortly scleroderma also falls in this group.

Lansbury speculates that inasmuch as invasion is a feature common to all neoplasms and since in some cases the collagen diseases disappear after the tumor is removed the association of the two may be caused by some factor which facilitates the invasion of malignant cells. This factor Lansbury suggests might be related to some hyaluronidase like substance secreted by malignant cells. The substance after entering the general circulation may interfere with the hyaluronate components of connective tissue and their enzymes and coenzymes. It would seem therefore good practice when a collagen disease occurs in an older person without a recognizable cause that studies should be made to detect a possible concealed neoplasm.

A Negro female aged sixty one years presently at the Bronx Municipal Hospital Center developed two years prior to admission a tingling sensation and pain in the hands and feet. At this time a chest x-ray disclosed active pulmonary tuberculosis and the patient was placed under treatment with streptomycin and isoniazid with considerable improvement in the pulmonary disease. A year later the pain in the extremities became worse. The skin of the fingers and toes showed atrophic changes with some deformity of the phalanges a picture of acrosclerosis. Two skin biopsies revealed subepithelial fibrillar fibrosis hyaline and some amyloid material also focal edema and vasculitis. The dermal changes were in keeping with scleroderma. The bones of the hands and feet showed roentgenologically deossification and soft tissue changes also calcification of blood vessels. At one of the staff conferences the problem was raised of the possible relationship of certain diseases of the skin and occult carcinoma. Three months later in the course of a careful examination a member of the house staff found a peculiar friable nontender granulomatous tissue mass in the floor of the patient's mouth. A biopsy revealed a papillary squamous cell carcinoma. Although the changes in the skin and the appearance of the carcinoma in the mouth of this patient may have been coincidental this experience is included among those reported by others to indicate that possibly there is an association of certain dermatoses and malignant neoplasms.

The records of the Montefiore Hospital in the first fifteen years contain four instances of scleroderma in association with malignant neo-

plasm In one case a man of fifty two with scleroderma had a complicating squamous cell carcinoma of the hands Another man of forty one had a fibrosarcoma of the left upper extremity engrafted on a sclerodermatous process The patient required amputation The neoplasm was found generalized in the body In a woman of forty three with scleroderma a pulmonary carcinoma was found In another woman of fifty six with an eighteen year history of scleroderma and Raynaud's disease a pleural effusion developed Autopsy revealed metastatic adenocarcinoma of the pleura probably originating in the gastric intestinal tract Zetchni and co workers reported three cases of scleroderma with diffuse interstitial fibrosis and primary cancer of the lungs In each instance the neoplasm was a terminal bronchiolar carcinoma The predisposition of patients with dermatomyositis to develop malignant neoplasm will be discussed later Chronically the two often progressing synonymously

In addition to collagen diseases Curtz draws attention to a number of other dermatoses which may be associated with intrathoracic and other neoplasms Pichlerdermoperiostosis has been found in association with bronchiogenic carcinoma This skin disorder is found predominantly in males and is characterized by skin changes which resemble those of acromegaly and roentgenologic findings in keeping with hypertrophic pulmonary osteoarthropathy Curtz also notes that with the development of erythema gstratum repens a disorder characterized by warty knobby pine granulations in the skin a primary or metastatic tumor may be found in the breast or lung Patients with generalized itching may later show signs of internal neoplasms and malignant lymphomas The itching which may be accompanied by urticarial wheals is probably due to allergens or toxins released by the tumor Acquired ichthyosis is encountered in patients with Hodgkin's disease or lymphosarcomas the cutaneous eruption being ascribed to liver damage and impairment of vitamin A metabolism

Curtz points out that while disappearance of the dermatosis after removal of the tumor and reappearance of the dermatosis with recurrence of the tumor point to some causal connection between tumor and dermatosis it would be wrong to assume the tumor to be the sole cause of the cutaneous eruption in every such instance The catabolic substrances of the neoplasm may serve as the trigger mechanism for skin predisposed to various pathologic processes by allergic or other factors

Scleroderma

tioned the disease may affect a wide variety of tissues and organs including the gastrointestinal tract particularly the esophagus the osseous system particularly the terminal phalanges of the fingers the skeletal muscles thyroid kidneys heart lungs and other structures (Figure 35) In addition the disease is often featured by the deposition of calcium salts in soft tissues a condition known as calcinosis The resulting induration and stiffening of the affected parts interferes with proper functioning of the organs leading to various symptoms and complications

A number of theories have been proposed to explain scleroderma In an exhaustive study based on an analysis of over 150 cases of scleroderma Lemm and co workers group the possible etiologic factors into four main cate-

For years dermatologists have been intrigued by a peculiar dermatitis encountered by patients usually young women possessing a peculiar leathery hard skin (scleroderma) Of late increasing attention is being paid to the condition by physicians it is large because of the realization that the skin lesions in this disease are only an outward expression of a profound systemic disturbance which may affect various organs and tissues

The change in skin texture is usually noted first in the hands the face neck and upper trunk Two major types of scleroderma are recognized a circumscribed and a diffuse progressive form The latter is in most instances a cutaneous manifestation of a systemic disease which according to Goetz should properly be called progressive systemic sclerosis As men-

gories (1) endocrine dysfunctions, (2) nervous system disturbances, (3) toxins, infections and trauma, and (4) vascular disease. As yet, no single explanation suffices. Scleroderma is commonly included among the collagen diseases and represents the least virulent member of the group.

PATHOLOGY

The morphological changes in scleroderma follow a fairly uniform pattern. The hardening of the skin and mucous membrane is the end result of a process which begins as a diffuse, nonpitting edema of the connective tissue. After the edema fluid absorbs, the stroma is replaced by fibrous tissue leading eventually to atrophy of the skin and underlying structures. An accompanying vascular disturbance manifests itself in arteriolar spasm and obliteration of small blood vessels with a corresponding reduction of blood flow to the parts. If the process affects the skin supplied by the digital arteries a fairly frequent accompaniment, the scleroderma may be associated with Raynaud's disease. The latter may precede recognizable sclerodermatous changes in the skin. A fully developed picture of scleroderma is featured by a mask-like face, the lips puckered so that smiling is difficult, the skin smooth and glistening with mottled pigmentation at times depigmentation, about the nose and mouth. The hands may show the stigmata of Raynaud's phenomenon with absence of digital phalanges.

The pulmonary lesions in scleroderma as in the other organs affected, is characterized by a sclerotic process which manifests itself either (1) as a diffuse interstitial fibrosis with thickening of alveolar walls, also obliteration of air spaces and compensatory emphysema, or (2) a similar picture accompanied with cystic sclerosis of the parenchyma, probably representing a further stage in the development of the disease. The cystic spaces are caused by hyaline degeneration of alveolar walls which become thinned out and rupture causing dissolution cysts. Bullous emphysema and bronchiectasis are occasionally seen. The pulmonary blood vessels, including the alveolar capillaries may be encased in a collagenous sheath with obliteration of capillaries and alveolar spaces. There is reason to suspect

that some cases of, so called, indeterminate forms of diffuse interstitial fibrosis and cystic disease of the lungs, of unknown origin, may be caused by sclerodermatous changes of these organs although skin changes may be absent. There are analogues for this state of affairs in sarcoidosis and several other diseases mentioned in this volume.

CLINICAL FEATURES

Hayman and Hunt found reports of seven cases of scleroderma in which symptoms referable to pulmonary involvement were present before the development of the skin disease or at a time when the cutaneous changes were so slight as to escape notice. Raynaud's phenomena preceded pulmonary symptoms in four of these cases, in the remaining three the pulmonary symptoms occurred as the initial manifestations of the disease. In two cases the time interval between the respiratory and cutaneous manifestations was more than two years. Prowse reports the case of a man of sixty-six who, one year before the appearance of clinical signs of scleroderma developed "pneumonia and pleurisy" on one side and, two weeks after recovery from this episode "pneumonia and pleurisy" on the other. The chest x-rays were interpreted as in keeping with chronic bronchitis and emphysema. The postmortem examination showed in addition to scleroderma of the skin, fingers, hands and lips a marked degree of interstitial fibrosis of the lungs and thickening of alveolar walls which were considered in keeping with scleroderma.

The symptoms of scleroderma of the lungs reflect the anatomic changes in the thoracic cage as well as the effects of stiffening of the lungs with resulting interference in the bellows action of the organs. Dry cough, dyspnea and cyanosis become increasingly severe as more alveolar epithelium is compromised in the fibrotic process. Orthopnea appears with a failing heart. Death may follow acute asphyxia or as a result of chronic cor pulmonale. The heart itself may of course, be the seat of sclerodermatous changes and contribute to the demise. At any stage, an intercurrent respiratory infection may terminate the course of the disease.

ROENTGENOLOGY

The roentgenological appearance of scleroderma of the lungs are not specific but they as some added significance in the light of the clinical findings. In the presence of emphysema the chest x ray may fail to reveal much deviation from the norm although widespread interstitial changes may be present in the organs. In uncomplicated cases both lungs show either fine or coarse striations affecting diffusely both organs. The changes are most pronounced in the inner

cystic changes the affected lungs may or may not show a fine honeycombing. In the late stages of the disease the pulmonary changes become even less distinctive roentgenologically. This is due to recurring pulmonary infections and suppuration. The latter is often due to aspiration of contents from the esophagus this organ being often involved in the process. Sooner or later the lungs reveal evidence of chronic passive congestion caused by a failing heart.

In an instance of scleroderma complicated by Raynaud's disease which I had occasion to follow on the wards of the Morrisania City Hospital and in the Chest Clinic the pulmonary markings appeared so striking and in keeping with the skin disease that after study the case was reported by Murphy, Kramm and Gerson as one of scleroderma with pulmonary fibrosis. This was the first case reported with a description of the pulmonary manifestations of the disease as seen roentgenologically. Unfortunately autopsy confirmation was not available. Subsequent studies by others including postmortem observations have confirmed the conclusions reached in this particular case. In recent years the possible presence of sclerodermatous changes in the lungs in patients with scleroderma of the skin has presented itself to me on a number of occasions. In fact in several I suspected scleroderma of the lungs although skin lesions were not demonstrable. But one cannot go as far as Pugh in claiming that in many cases the roentgenologic diagnosis of pulmonary scleroderma can be made without knowledge of the clinical

picture. Even in the presence of scleroderma of the skin it is most difficult to correlate the markings in the lungs with the dermal changes because of the complicating factors previously mentioned.

In the following case the initial symptoms were in keeping with an acute nonbacterial bronchopneumonia. Serial chest x rays revealed increasing diffuse interstitial fibrosis of the lungs. At the same time the patient developed signs of scleroderma with Raynaud's phenomenon also evidence of lupus erythematosus the diagnosis of the latter being confirmed by the presence of L. E. cells in the blood on repeated occasions. The case demonstrates not only the pulmonary findings in scleroderma but also the association of the latter with lupus erythematosus a kinship stressed in Chapter 6.

Case 23 Female—Age 39

The patient was admitted to the Montefiore Hospital on Dr. Sol Biloon's service in December 1952 with fever, dyspnea and physical signs pointing to an acute pneumonia of one day's duration. A bedside chest x ray taken on the day of admission revealed massive infiltrations involving both lungs with little air containing tissue to be seen. There was moderate enlargement of the heart (Figure 36B). The impression was that of congestive heart disease and bronchopneumonia since the patient had had a seizure of coronary occlusion four years previously for which she had been treated with low salt diet and diuretics.

The patient received large doses of penicillin and streptomycin but the temperature remained elevated for some time and declined slowly. A week after admission the patient experienced a sudden chill the temperature rose and at this time the patient had pain and tenderness in the abdomen as well as evidence of coldness of the extremities and peripheral cyanosis. The patient experienced several additional seizures of this nature. Of significance in the laboratory findings was the presence of a high degree of macrocytic anemia and a relative leukopenia. The patient improved slowly and was discharged a month after her admission.

At home the patient soon developed pain, swelling and stiffness of the hands and, at times, pain and cramps in the legs. The patient was readmitted to the hospital six months after her discharge be-

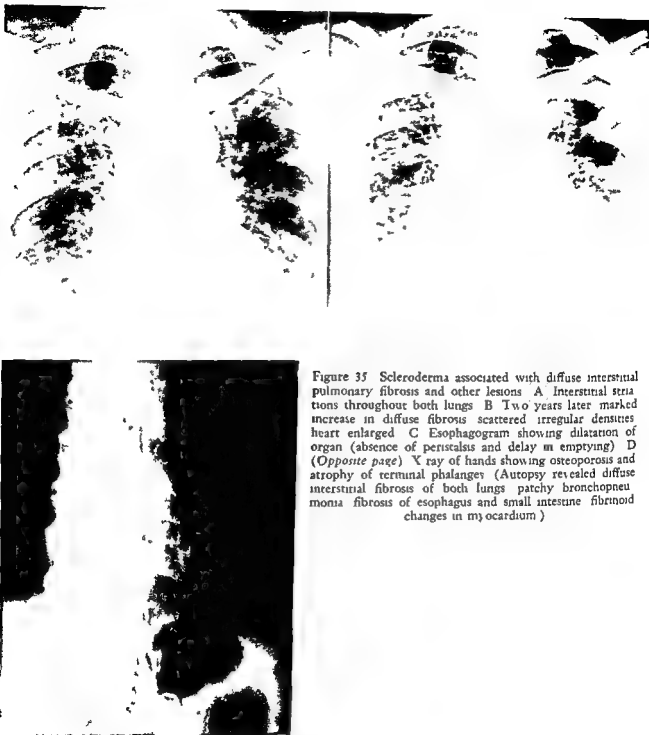


Figure 35 Scleroderma associated with diffuse interstitial pulmonary fibrosis and other lesions A Interstitial striations throughout both lungs B Two years later marked increase in diffuse fibrosis scattered irregular densities heart enlarged C Esophagogram showing dilatation of organ (absence of peristalsis and delay in emptying) D (Opposite page) X ray of hands showing osteoporosis and atrophy of terminal phalanges (Autopsy revealed diffuse interstitial fibrosis of both lungs patchy bronchopneumonia fibrosis of esophagus and small intestine fibrinoid changes in myocardium)

cause of the sudden reappearance of chills, fever and sweating. The physical examination revealed a chronically ill looking woman who appeared older than her stated age. There was atrophy and swelling of the fingers and spindling of the terminal phalanges. The mouth was pinched and the skin over the forehead tight. There was a scaling erythema

tous rash over the V of the neck with patchy involvement of the trunk and extremities (Figure 36A). The erythema became more marked after exposure to light. The patient offered the additional information that she had noted cold hands even in warm weather and at times the fingers turned bluish in color.

Examination at this time revealed deformity of the finger joints, dullness and rales at the bases of the lungs and moderate liver enlargement. On several occasions pleural and pericardial friction rubs were heard. The chest x-rays revealed increasing diffuse fibrosis of both lungs (Figures 36C and D). Significant laboratory findings included the presence of anemia, leukopenia and positive TTT tests of the blood on repeated occasions. The patient

continued to have low grade fever and showed sensitivity reactions to blood transfusions and drug medication. The final diagnosis was scleroderma associated with Raynaud's phenomenon, lupus erythematosus, rheumatoid arthritis and arteriosclerotic heart disease. Although not fully recovered, the patient left the hospital. Two months later she died suddenly of what was presumed to be an acute coronary artery seizure.

Dermatomyositis

This disease has certain features in common with lupus erythematosus and scleroderma but in other significant respects shows individual characteristics. Dermatomyositis affects more often males of advanced age. The disease involves the skin, subcutaneous tissues and muscles. It may run an acute, but more often a chronic course. The onset is insidious with fatigue, muscle pain, weakness and lassitude. In time, cutaneous changes appear with puffiness of the face and an erythematous rash involving the neck, ears, chest and shoulders. The erythema affects chiefly the dorsum of the hands at the phalangeal joints

the fingers in time becoming stiff and painful. The muscle weakness is bilateral and symmetrical; in advanced stages the muscle weakness may interfere with deglutition and respiration leading to aspiration pneumonia. Histologically, the affected parts reveal changes of a nonspecific nature consisting of edema of interstitial tissues, lymphocytic infiltration and necrosis of muscle fibers. The changes lead eventually to atrophy and contractures.

The pulmonary changes in dermatomyositis are not a feature of the disease. A careful search of the literature does not reveal any reported in-



Figure 35D (See legend on opposite page)

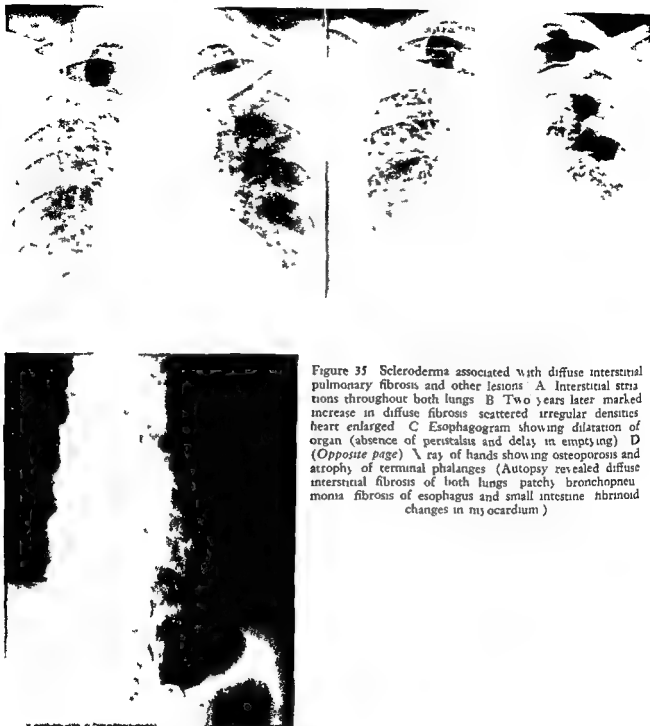


Figure 35 Scleroderma associated with diffuse interstitial pulmonary fibrosis and other lesions: A Interstitial striations throughout both lungs B Two years later marked increase in diffuse fibrosis scattered irregular densities heart enlarged C Esophagogram showing dilatation of organ (absence of peristalsis and delay in emptying) D (Opposite page) X ray of hands showing osteoporosis and atrophy of terminal phalanges (Autopsy revealed diffuse interstitial fibrosis of both lungs patchy bronchopneumonia fibrosis of esophagus and small intestine fibrinoid changes in myocardium)

cause of the sudden reappearance of chills fever and sweating. The physical examination revealed a chronically ill looking woman who appeared older than her stated age. There was atrophy and swelling of the fingers and spindling of the terminal phalanges. The mouth was pinched and the skin over the forehead tight. There was a scaling erythema

tous rash over the V of the neck with patchy involvement of the trunk and extremities (Figure 36A). The erythema became more marked after exposure to light. The patient offered the additional information that she had noted cold hands even in warm weather and at times the fingers turned bluish in color.

Examination at this time revealed deformity of the finger joints, dullness and rales at the bases of the lungs and moderate liver enlargement. On several occasions pleural and pericardial friction rubs were heard. The chest x rays revealed increasing diffuse fibrosis of both lungs (Figures 36C and D). Significant laboratory findings included the presence of anemia, leukopenia and positive I-I tests of the blood on repeated occasions. The patient

continued to have low grade fever and showed sensitivity reactions to blood transfusions and drug medication. The final diagnosis was scleroderma associated with Raynaud's phenomenon, lupus erythematosus, rheumatoid arthritis and arteriosclerotic heart disease. Although not fully recovered the patient left the hospital. Two months later she died suddenly of what was presumed to be an acute coronary artery seizure.

Dermatomyositis

This disease has certain features in common with lupus erythematosus and scleroderma but in other significant respects shows individual characteristics. Dermatomyositis affects more often males of advanced age. The disease involves the skin, subcutaneous tissues and muscles. It may run an acute, but more often a chronic course. The onset is insidious with fatigue, muscle pain, weakness and lassitude. In time cutaneous changes appear with puffiness of the face and an erythematous rash involving the neck, ears, chest and shoulders. The erythema affects chiefly the dorsum of the hands at the phalangeal joints

the fingers in time becoming stiff and painful. The muscle weakness is bilateral and symmetrical. In advanced stages the muscle weakness may interfere with deglutition and respiration, leading to aspiration pneumonia. Histologically, the affected parts reveal changes of a nonspecific nature consisting of edema of interstitial tissues, lymphocytic infiltration and necrosis of muscle fibers. The changes lead eventually to atrophy and contractures.

The pulmonary changes in dermatomyositis are not a feature of the disease. A careful search of the literature does not reveal any reported in-



Figure 35D (See legend on opposite page)

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

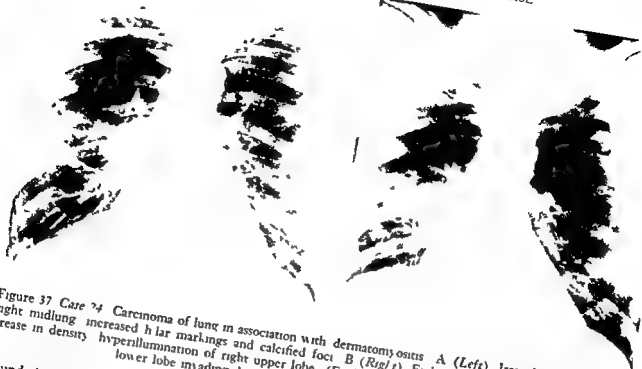


Figure 37 Case 74 Carcinoma of lung in association with dermatomyositis A (Left) Irregular infiltrations in right midlung increased hilar markings and calcified foci B (Right) Eighteen months later considerable increase in density hyperillumination of right upper lobe (Exploratory thoracotomy revealed carcinoma of right lower lobe invading diaphragmatic pleura giant bulla in upper lobe)

found shrunken with induration and distention of the subpleural lymphatics. The middle lobe was not involved. There was a large emphysematous bulla occupying the right upper lobe. The parietal pleura was found studded with metastases especially over the diaphragm. The hilum was indurated with neoplasia. Because of the extensive involvement a resection was impossible. Histologic examination of a piece of parietal pleura revealed coalescing metastatic nodules.

Following operation the patient continued to complain of muscular weakness pain in the arms also dyspnea nausea and vomiting. The erythematous rash noted previously now covered the upper chest arms face as well as hands. The patient was admitted to the Montefiore Hospital where a muscle and skin biopsy was obtained from the deltoid

region. Histologic examination of the specimen revealed atrophy of epidermis with fragmentation focal disruption and dissolution of the immediately adjacent corium. There was some thickening of the collagen of the deeper layers of the corium. There was edema of the vessel walls and perivascular collections of inflammatory cells consisting of lymphocytes and neutrophils. The vessels affected were generally of arteriolar and precapillary size. Individual muscle fibers had lost their coarse striations. There was interstitial inflammatory reaction in the muscles the cellular population of which was largely perivascular. The tissue changes appeared consistent with the clinical diagnosis of dermatomyositis. The patient went rapidly downhill and died.

Acanthosis Nigricans

This disease is characterized by the presence of darkly pigmented furrowed areas arranged symmetrically on the exposed surface of the body especially in the axillary inframammary antecubital and crural folds. The hyperkeratotic skin and proliferation of epithelium often results

in small warty growths. Two forms of acanthosis nigricans are recognized (1) a juvenile or benign form occurring in young people especially at the time of puberty and (2) an adult or malignant form occurring in later years. The latter is associated with cancer of viscera in up

proximately 50 per cent. Because of the high incidence of malignant neoplasms especially of abdominal viscera some authorities hold that a diagnosis of acanthosis nigricans in an individual of advanced age warrants an exploratory laparotomy.

In a review of 393 cases of acanthosis nigricans reported in the literature up to 1943 Carth found the association of cancer reported in approximately one half 93 per cent of the latter being abdominal with carcinoma of the stomach accounting for almost 70 per cent. Carcinoma of the lung was reported in only three cases including one described by Levin and Behrman of a man treated at the Montefiore Hospital. The remaining two included one discovered incidentally by Dore and one reported by Petrucci de Galatz. In 1950 Spear reported an additional case of acanthosis nigricans in a fifty year old white man in association with anaplastic carcinoma of the lung.

Because of the rarity of carcinoma of the lung in association with acanthosis nigricans the fol-

lowing case which came to my observation is worth citing.

Case 25 Male—Age 42

The patient lithographer developed a rash under the chin. Later he noted that the skin on the arms pits and in the groin became dark and stiff (Figure 38A). The patient was seen by several dermatologists who diagnosed the condition as acanthosis nigricans. Of interest in the patient's past history was the fact that since the age of twenty three he had developed gradual loss of eyesight and a sister was also afflicted with loss of eyesight the cause of which could not be determined. When I examined the patient the symptoms were moderate cough and bloody expectoration. The skin in the folds of both axillae and groins was dry, darkly pigmented and ridged with minute papillae projecting above the surface. A chest x ray revealed a large homogeneous spherical density occupying the entire superior aperture of the thorax (Figure 38B). Biopsy of a supraclavicular lymph node showed squamous cell carcinoma. Radiotherapy was applied but the patient went downhill and died three months later.



Fig. 38. A. C.

darkly pigmented
right upper lobe

Scleredema

This disease was first described by Buschke in 1900. In 1932 Epstein gave the first comprehensive review of the subject. Scleredema may follow or be precipitated by acute infections such as scarlet fever, influenza or pharyngitis or the disease may be ushered in with fever and rheumatic symptoms. Several days or weeks after the subsidence of the acute infection the patient develops a rapidly progressive nonpitting edema of the face chiefly about the eyelids which become puffed up. Leinwand described the waxy appearance of the face as if the skin were in a paraffin bath. The edema spreads to the neck, shoulders, arms and abdomen. The disease undergoes spontaneous remission within a variable period of months. In contrast to scleroderma in the edematous stage with which it may be confused scleredema spares the hands and feet and almost invariably resolves without causing permanent damage. However acute dermatomyositis myxedema as well as scleroderma may present problems in differential diagnosis. The systemic nature of scleredema has been stressed

by Vallee, O'Leary and co-workers, Leinwand and others.

The nature of the pleuropulmonary changes which may be present in scleredema have not been studied in detail because the disease is seldom fatal. However pleural effusions are often encountered in association with pericardial, peritoneal and joint effusions. A rare instance of generalized scleredema with autopsy findings reported by Leinwand revealed in addition to fluid in both pleural cavities diffuse edematous changes of the lungs. Many of the viscera had a peculiar rubbery consistency. Microscopic examination revealed swelling of the collagen with separation of the bundles resulting in clear spaces. There was a notable absence of inflammatory reaction. In four patients with scleredema Vallee noted pleural fluid in two, one had massive effusions in both cavities and the other had in addition a pericardial effusion. The fluid disappeared with remission of the cutaneous disease. Vallee believes that intrathoracic effusions are an intrinsic feature of the disease.

Sjogren's Disease

In 1933 and in later publications Sjogren described a syndrome characterized by pronounced dryness of the mucous membranes due to inadequate secretion of glands especially of the salivary and lacrimal glands. Later studies revealed that the condition may also involve the glands of the respiratory tract, stomach, sweat glands and vaginal mucosa. The major pathological features consist at first of a lymphocytic cellular infiltration producing glandular enlargement and later parenchymal atrophy resulting in impaired function. Eventually both parenchyma and cellular infiltrate disappear and are replaced by a fibroadipose tissue. The participation of the lacrimal and salivary glands may present a picture simulating Mikulicz disease. In fact some authors prefer the term Mikulicz-Sjogren Disease. It is suspected that both conditions are related to sarcoidosis and that all three are manifestations of the same process. The reduced salivation and keratinization

and the resulting dryness of the nose, pharynx, stomach, trachea and bronchi and other mucous membranes may produce distressing symptoms.

Sjogren's disease is believed to be a congenital defect since members of the same family have been found affected. The precipitating factor may be an endocrine disturbance, the condition being particularly frequent in women at the time of the menopause. Sjogren in one of his early communications stated that the mucous membrane lesions are part of a generalized disease. The frequent association of rheumatoid arthritis is in keeping with such a concept. A variable degree of success has been reported with the use of estrogenic and androgenic preparations, corticotropin hormones, cortisone, cholinergic drugs, pilocarpine and other medicaments. The disease is refractory to treatment.

Noteworthy from the view point of the present discussion is the fact that dryness of the bronchial mucosa and associated obstructive phenomena

may cause pulmonary changes of a granulomatous character associated with low grade inflammation. Ellman and Weber described the case of a woman, with Sjogren's disease, who developed bilateral dry pleurisy. Later, she was found to have abnormal physical findings at both lung bases. This was associated with a roentgen picture simulating sarcoidosis. Through the cour-

tesy of Dr Henry K. Taylor, I had an opportunity to see the chest x rays of a patient with clinical features of Sjogren's disease. The film revealed diffuse fibrosis and emphysema of both lungs, especially the right upper. In this case, as in the one reported by Ellman and Weber, the patient had also been diagnosed at first as sarcoidosis.

Bibliography

DISEASES OF THE SKIN AND MALIGNANT TUMORS

- CLUTH H O. Dermatoses and Malignant Internal Tumors. *Arch Dermat* 71:95 1955
 LANSBURY J. Collagen Disease Complicating Malignancy. *Ann Rheumat Dis* 12:301 1953
 VAGLE J. La Pachydermoperiostose. *Ann med* 57:157 1950
 ZATCHEL J, CAMPBELL W N and ZARAFONETIS C J D. Pulmonary Fibrosis and Terminal Bronchiolar (Alveolar Cell) Carcinoma in Scleroderma. *Cancer* 6:1147 1953

SCLERODERMA

- ARONSON M M and WALLERSTEIN L. Protean Nature of Scleroderma—With a Note on Pulmonary Changes. *New York State J Med* 50:2723 1950
 BEISELMAN P M, GOLDNER F JR, BAYLES T M. Progressive Systemic Sclerosis (Scleroderma). *New England J Med*, 249:45 1953
 CHURCH R E. Cystic Pulmonary Fibrosis in Generalized Scleroderma. Report of Two Cases. *Lancet* 1:397 1950
 DOSIGROVSKY A. Progressive Scleroderma of the Skin with Cystic Sclerodermal Changes of the Lungs. *Arch Dermat & Syph* 55:1 1947
 ELLMAN P and CUDKOWICZ L. Pulmonary Manifestations in the Diffuse Collagen Diseases. *Thorax* 9:46 1954
 GOETZ R H. The Pathology of Progressive Systemic Sclerosis (Generalized Scleroderma) with Special Reference to Changes in the Viscera. *Clin Proc* 4:337 1945
 HAYMAN L D and HUNT R E. Pulmonary Fibrosis in Generalized Scleroderma. *Dis Chest* 21:691 1952
 HEKTOFF L. Diffuse Scleroderma Associated with Chronic Fibrous Changes in Thyroid and Great Diminution in Amount of Thyroidin. Increase in Chromophile Cells and of Colloid in Hypophysis. *JAMA* 78:1240 1897
 HUTCHESON J M. The Visceral Lesions of Scleroderma. *Virginia M Month* 78:419 1951
 JACKMAN J. Roentgen Features of Scleroderma and Acro sclerosis. *Radiology* 40:163 1943
 KIERLAND R R., and HINES E A JR. Cortisone and Corticotropin (ACTH) in Treatment of Scleroderma. *Arch Dermat & Syph* 64:549 1951
 LEINWAND I, DUNAY A W and RICHIER M N. Scleroderma (Based on a Study of Over 150 Cases). *Ann Int Med*, 41:1003 1954
 LINENTHAL H. Observations Concerning Pulmonary Fibrosis in Raynaud's Disease. *New England J Med* 227:435 1942

- LINENTHAL H and TAYLOR R. Pulmonary Fibrosis in Raynaud's Disease. *New England J Med*, 224:682 1941
 LLOYD W C and TOWNIN, R D. Pulmonary Fibrosis in Generalized Scleroderma. *Thorax* 3:241 1948
 MAHRER P R, IVANS J A., and STEINBERG, I. Scleroderma: Relation of Pulmonary Changes to Esophageal Disease. *Ann Int Med*, 40:92 1954
 MURPHY J R, KRAHIN P and GERSON M J. Scleroderma with Pulmonary Fibrosis. *JAMA*, 116:499 1941
 PROWSE C B. Generalized Scleroderma with Intestinal Involvement. *Lancet* 1989 1951
 PUGH D G. Roentgenologic Manifestations of Scleroderma. *Am J M Sc* 216:571 1948
 PUGH D G, KYLE W F and MARGLIES H. Scleroderma with Involvement of the Viscera. Report of Case. *Proc Staff Meet Mayo Clin* 20:410 1945
 ROTHSCHILD S and WALKER M. Scleroderma. *Al Clin North America* 33:55 1949
 SHILFORD W H, SEAMAN W B and GOLDMAN A. Pulmonary Manifestations of Scleroderma. *Arch Int Med* 92:85 1951
 SPAIN M M. The Pulmonary Manifestations of Scleroderma. An Anatomic Physiological Correlation. *Ann Int Med* 32:152 1950
 WILEY J E M, CONLON V and BRADLEY R. Pulmonary Fibrosis in Scleroderma. *Brit J Dermat* 61:324 1949

DERMATOMYOSITIS

- BRENNER M J and LOBBACK R V JR. Dermatomyositis as an Index of Malignant Neoplasm. Report of a Case and Review of the Literature. *Ann Int Med* 34:169 1951
 CHURCH R E. Discussion of case by Forman
 COTTEL C E. Dermatomyositis and Malignant Neoplasm. *Am J M Sc* 724:160 1952
 CLIFTS A C, BLAYLOCK H C and HARRELL E R JR. Malignant Lesions Associated with Dermatomyositis. *JAMA* 150:844 1952
 DONIZALSKI C A and MORGAN, V C. Dermatomyositis: Diagnostic Features and Therapeutic Pitfalls. *Am J Med*, 19:370 1955
 FORMAN L. Dermatomyositis with a Past History of Carcinoma of the Ovaries. *Proc Roy Soc Med* 44:880 1951
 KEEL H. Dermatomyositis and Systemic Lupus Erythematosus. *Arch Int Med* 66:319 1940
 KEEL, H. The Manifestations in the Skin and Mucous Membranes in Dermatomyositis with Special Reference to the

- Differential Diagnosis from Systemic Lupus Erythematosus *Ann Int Med*, 16:828, 1942
- McCOMBS, R. P., and MacMATHON, H. E. Dermatomyositis Associated with Metastasizing Bronchogenic Carcinoma *M Clin North America*, 31:1148, 1947
- QUIROGA, M. I., and BOTTRICH, H. Dermatomyositis and Visceral Cancer *Prensa med argent*, 36:2107, 1949, abstracted *JAMA*, 142:1028, 1950
- SHEARD, C., JR. Dermatomyositis *Arch Int Med*, 83:640, 1951
- COCHRAN, T., and ALEXANDER, J. O. D. Acanthosis Nigricans *Brit J Dermat*, 63:225, 1951
- CURTI, H. L. Cancer Associated with Acanthosis Nigricans *Arch Surg*, 47:517, 1943
- DORE, — Discussion of Case of Acanthosis Nigricans by NIXON *Brit J Dermat*, 26:94, 1914
- LEVIN, O. L., and BEHRMAN, H. T. Acanthosis Nigricans Associated with Carcinoma of the Lung *Arch Dermat & Syph*, 46:54, 1942
- MUKAI, T. Acanthosis Nigricans *Acta Dermat*, 14:447, 1929
- PETRINI, DE GALATZ. Acanthosis Nigricans *Bull Soc franç, de dermat et syph*, 20:114, 1909
- SPEAR, P. W. Acanthosis Nigricans Associated with Cancer of the Lung *J Thoracic Surg*, 20:304, 1950
- der Berliner Gesellschaft für Dermatologie *Arch Dermat u Syph*, 53:383, 1900
- EPSTEIN, N. N. Scleroderma in Adulthood (Buschke) *JAMA*, 99:820, 1932
- LEINWAND, I. Generalized Scleroderma. Report with Autopsy Findings *Ann Int Med*, 34:226, 1951
- MURSON, L. L. Scleroderma *Am J Med*, 9:707, 1950
- OLEARY, P. A., WAISMAN, M., and HARRISON, M. W. Scleroderma Adulthood. *Am J Med Sc*, 199:418, 1940
- VALLEE, B. L. Scleroderma A Systemic Disease *New England J Med*, 235:207, 1946
- CADELL, B. S., and GURLING, K. J. Observations on the Pathology of Sjögren's Syndrome *J Path & Bact*, 68:137, 1954
- COOPERMAN, H. O. Sjögren's Syndrome - Secretory Inhibitor Syndrome *Am West Med & Surg*, 4:344, 1950
- COVERDALE, H. Some Unusual Cases of Sjögren's Syndrome *Brit J Ophth*, 32:669, 1948
- ELLMAN, P., and WEBER, F. P. Sjögren's Disease, with Dryness of the Bronchial Mucosa and Uncertain Lung Lesion *Brit M J*, 1:304, 1949
- KENNY, F. E., and LONG, J. E. Sjögren's Syndrome. Review of Literature and Report of a Case *JAMA*, 155:435, 1954
- SJÖGREN, H. Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tränendrüsen) *Acta Ophth Supp*, 2:1, 1933

ACANTHOSIS NIGRICANS

SJÖGREN'S DISEASE

SCLERODEMA

BUSCHKE, A. Vorstellung eines Falles von Sklerodem vor

Diseases of the Skin and Mucous Membranes (Concluded)

Sarcoidosis

INTRODUCTION

SARCOIDOSIS IS PROBABLY the best example of the thesis under consideration, namely, the lungs may not only mirror an internal disturbance, but they may be the sole organs found involved in what is generally acknowledged as a systemic disease. Sarcoidosis was originally described by Hutchinson and later by Boeck in 1899 as a dermatologic disorder. The latter designated the condition sarcoidosis, because the histologic changes resembled sarcomatous lesions. In time, Boeck's sarcoid was accepted in dermatology as a distinct entity. In 1914, Schaumann expressed the view that Boeck's sarcoid, or benign milium, lipid as Boeck subsequently redesignated the disease, was a systemic affliction, a benign lymphogranuloma, which may involve many organs of the body, especially the group comprising the reticuloendothelial system. But, in spite of the fact that sarcoidosis is neither a sarcoma nor a lupus-like disorder, nor primarily a skin disease, the designation sarcoid, has been retained chiefly for want of a better nomenclature.

Unaware of the singleness of the disease, earlier investigators in various branches of medicine, including neurologists, ophthalmologists, endocrinologists and pediatricians described, from time to time, various facets of sarcoidosis as distinct syndromes of which there are about two dozen listed in the literature. The more frequent eponyms under which sarcoidosis has been described include Besnier-Boeck-Schaumann's disease (systemic sarcoidosis), Heerfordt's disease (uveoparotid fever), Jungling's disease (ostitis tuberculosa multiplex cystica) and Mikulicz' dis-

ease (lacrimal and salivary gland involvement). In recent years the literature on the subject has reached voluminous proportions largely due to the interest focused on the disease following the introduction of routine chest roentgenography in the examination of apparently healthy persons. Intrathoracic sarcoidosis is currently a favorite topic of discussion among physicians interested in diseases of the chest. It is now established that Boeck's sarcoid, originally described as a skin disease, may affect various organs and tissues of the body without necessarily implicating the skin, in fact, in systemic sarcoidosis the skin is more likely to be spared.

INCIDENCE AND DISTRIBUTION

Among uncommon diseases sarcoidosis is frequent, especially the intrathoracic form. In 1948 Freiman found more than 1,000 cases of sarcoidosis and related syndromes reported in the literature. The disease has long outgrown the stage of individual case reports unless the latter deal with unusual features or are concerned with basic etiologic, immunologic or therapeutic problems. The earlier descriptions of the disease stemmed largely from Scandinavian and European countries, in recent years a sizable literature on the subject has accrued in America. A comprehensive monograph on sarcoidosis by Longcope and Freiman, published in 1952, is based on a combined investigation of 160 cases, including thirty examined at autopsy, from two institutions alone.

Sarcoidosis affects chiefly adults of the third and fourth decades of life but infants and aged are not spared. Instances of sarcoidosis have been reported in members of the same family,

including identical twins and running a similar course. The disease is found with about equal frequency in the two sexes possibly more often in females. In the Scandinavian countries, England and on the Continent, Nordics are mainly affected. In the United States, Negroes are particularly vulnerable, especially those born in the southeastern states. An analysis of approximately three hundred cases of sarcoidosis encountered in the armed forces of the United States revealed sixteen times as many cases of the disease in Negroes as in Whites. Other features of the epidemiology of the disease will be discussed in conjunction with the significance of negative tuberculin reactions usually encountered in sarcoidosis.

PATHOLOGY

In 1944 Pinner and I reported a case of systemic sarcoidosis the course of which could be followed from childhood to the death of the patient at the age of twenty-five. The post mortem findings of this patient and of twenty-five additional autopsied cases reported by others were described in detail. The literature at the time of this writing, 1954, contains reports of approximately 150 autopsied cases. Ricker and Clark described twenty-two cases of sarcoidosis with autopsy findings culled from the files of the Army Institute of Pathology. Inasmuch as some of the patients described in the series had died of gunshot and other traumatic injuries and in two-thirds the disease had been unsuspected until the postmortem examination, the study by these investigators is unusually instructive with respect to the early developmental phases of the disease.

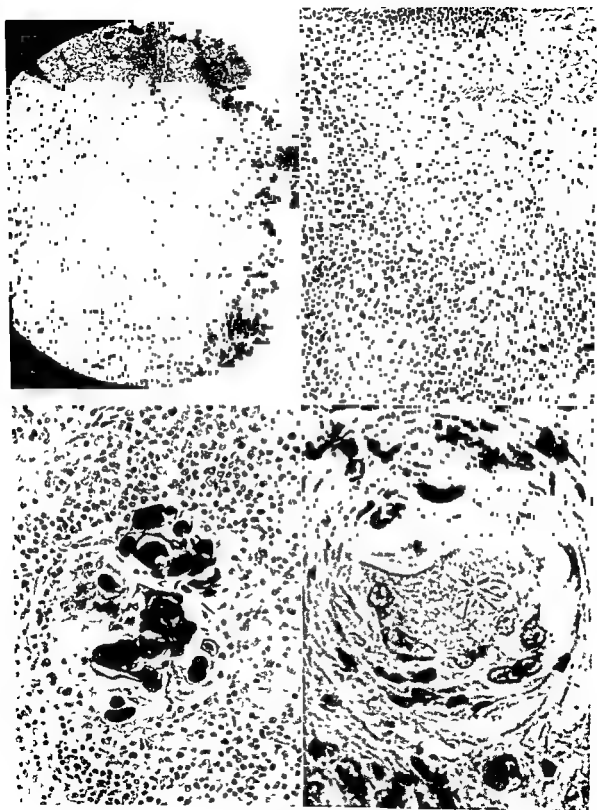
The histologic features of sarcoidosis irrespective of the organs or tissues involved are of a monotonous consistency. In its classical form the disease is characterized by tubercle-like structures composed of epithelioid cells, small numbers of lymphocytes and giant cells of the Langhans type (Figure 39A and B). Macroscopically aggregates of these tubercles reveal themselves

as disseminated nodules in the affected tissue or organs. These cold miliary tubercles were considered at one time to be an expression of noncaseating tubercles. Pinner, an early advocate of this theory, changed his views in his later years, preferring the noncommittal term *sarcoidosis*.

According to Ricker and Clark, the earliest lesion of sarcoidosis is recognizable especially in the lymph nodes in areas of widening of the lymphoid sinuses and hyperplasia of reticulum cells. The affected tissue soon becomes the seat of discrete epithelioid tubercles which are arranged in clusters of approximately the same stage of development. There is an absence or a minimal degree of necrosis and no acid fast organisms can be cultured from the tissues. The last mentioned feature is decisive in the differentiation of sarcoidosis from tuberculosis unless the latter is superimposed on the former. In its protracted course sarcoidosis may affect various organs and tissues of the body at different times so that signs of progression and recession may be present concurrently.

In the process of healing the tubercles merge and lose their identity eventually undergoing fibrosis and in many instances diffuse hyalinization, the nodules becoming acellular scars. In the lungs, as in other organs which may be involved, one cannot differentiate the diffuse interstitial fibrosis of sarcoidosis from other forms of fibrosis unless one is familiar with the clinical findings and the results of histological and immunological studies. It should be emphasized that even when the histologic picture corresponds entirely with that of sarcoidosis, a diagnosis cannot be made with certainty inasmuch as epithelioid cell granulomas may be caused by beryllium compounds, silicosis and other agents. This aspect will be discussed more fully later. The uncomplicated sarcoid lung in which the disease had been evolving for some time shows grossly diffuse fibrosis, the parenchyma studded with grayish nodules. There is a variable degree of bronchiectasis, emphysema and bleb formation. On rare occasion

Figure 39. Sarcoidosis: histologic features. A (Upper left) Noncaseating epithelioid tubercles with scattered giant cells. B (Upper right) Detail of tubercles. C (Lower left) (Doubly refractile) Schaumann corpuscle in ruptured giant cell. D (Lower right) Asteroid body in giant cell.



(See legend on opposite page)

the latter may lead to spontaneous pneumothorax. There are occasionally smooth-walled cavities which show no caseation or sarcoid changes in the walls, the exact origin of which is difficult to ascertain.

In addition to the tubercle-like structures mentioned, the histopathology of sarcoidosis is occasionally featured by the presence of giant cell inclusions. These intracellular inclusion bodies were first described by Schaumann in 1941. The "Schaumann corpuscles" are refractile, stratified and, in some cases, calcific bodies (Figure 39C). They are more apt to be found in lymph nodes but may also be present in other organs, including the lungs. In 1944, Friedman described an asteroid form of inclusion body in the spleen of a patient with sarcoidosis (Figure 39D). Others have encountered such asteroid or radial bodies in other organs also. Schaumann corpuscles have been found in beryllium lesions and asteroid bodies have been found in leprosy, torulosis, histoplasmosis and in foreign body granulomas.

Cunningham found stellate inclusions in giant cells in three types of tissue response: in association with foreign body reaction, tuberculoid granulomatous inflammation and in acute and chronic inflammation and repair. The inclusion bodies found in sarcoidosis are therefore not specific for any disease. Various opinions have been expressed as to the components of these inclusion bodies. Teilum found paramyloid deposits in the reticuloendothelial cells of sarcoidosis similar to those seen in patients with disseminated lupus erythematosus and in those with atypical and experimental amyloidosis. This investigator considers Schaumann corpuscles the result of hyperglobulinotic precipitates in the cytoplasm of the reticuloendothelial cells.

ETIOLOGY

It is beyond the scope of these pages to discuss at length the possible cause or causes of sarcoidosis. Only those aspects bearing on the problem of diagnosis will be mentioned. In an exhaustive review Rosentberg comes to the conclusion that sarcoidosis, if it is an infectious disease, is most likely caused by a new agent, a disease *in genere*. It is difficult to conceive of sarcoidosis being a variant of any known existing disease, certainly

not tuberculosis, a belief still prevailing in some quarters. Rosentberg points out the importance of distinguishing between systematized sarcoidosis and the, multiple caused, pattern reaction known as sarcoid inasmuch as the latter constitutes a commonplace type of tissue response to injury shared by other diseases. Sarcoid like granulomas may be found in brucellosis, chronic disseminated histoplasmosis, syphilis, tularemia, balstomycosis, leprosy, and other fungous infections, berylliosis and several other conditions.

As mentioned, the sarcoid tubercle resembles superficially the tubercle of tuberculosis but differs from the latter in the paucity or lack of necrosis but more significantly in the fact that pathogenic acid fast bacilli cannot be demonstrated in the affected tissues. Early in the course of sarcoidosis, a coexisting active tuberculosis is rare, late in the disease tuberculosis is found in about 15 per cent of autopsied cases. Interestingly enough, in a case of systemic sarcoidosis with terminal tuberculosis, studied by Pinner and myself, numerous lung sections revealed histologically both noncaseated and caseated tubercles containing giant cells but only in the noncaseated tubercles were occasional calcific bodies found some of which were ring shaped. Acid fast bacilli were readily demonstrable in the caseated lesions in the lungs, liver, kidneys, spleen and adrenals. In more than fifty noncaseated, epithelioid tubercles in the lung, liver and spleen no acid fast bacilli could be found. A search for acid fast bacilli in lymph node lesions was entirely unsuccessful.

Because the sarcoid granuloma resembles histologically tubercle and, in the late stages of sarcoidosis, tuberculosis may appear, has led some investigators to the opinion that the two are synonymous. However, Snapper points out that patients with diabetes mellitus, Hodgkin's disease and leprosy are also prone to develop tuberculosis yet they are not caused by the same agent. Of particular significance from a clinical standpoint is the fact that sarcoidosis has a predilection for organs and tissues which are seldom the seat of tuberculosis, *viz.*, skin, eyes, salivary glands, cranial nerves, pituitary body, myocardium, phalanges and bone marrow. On the other hand, the

serous membranes, which are often involved in tuberculosis, are comparatively immune to sarcoidosis. Pleural effusion is seldom seen in sarcoidosis unless the disease is complicated by tuberculosis or heart failure. Inclusion bodies are rarely, if ever, seen in tuberculosis.

In addition to tuberculosis, several other possible etiologic agents have been suggested. Torrell finds a close parallelism between sarcoidosis and pulmonary bronchomycoses, especially moniliasis. This author therefore suspects a fungus as a possible cause. Lofgren and Lundback were able to isolate a virus from every one of six cases of sarcoidosis investigated. Preliminary tests showed that the virus probably belonged to the influenza-mumps Newcastle disease group of viruses. Inasmuch as the disease has a predilection for the lungs, eyes, tonsils and salivary glands, an inhalational infection is of course a possibility. But it should be noted that when the lungs are involved in sarcoidosis the disease is invariably bilateral and symmetrical, a distribution that does not conform to aerogenous infection.

Current opinion is leaning to the view that sarcoidosis is a nonspecific disease probably of an allergic nature. Suggestive indices, pointing to this concept are obtained in cases such as those reported by Bjerkelund also Wyers and co-workers who described instances of sarcoidosis featured by migratory polyarthritis, erythema nodosum, fever and hilar adenopathy. The response of sarcoidosis to ACTH and cortisone treatment, although often temporary, is also significant. Finally, a number of experimental observations, relating to altered immunologic reactions, are on record which bespeak a nonspecific disease related to sensitivity. According to this concept Boeck's sarcoid is believed to be a syndrome resulting from the individual's peculiar reaction to various agents. Refsum reported cases of quartz granuloma or quartz sarcoid, and of sarcoid formation around foreign bodies other than quartz in patients with sarcoidosis. This investigator also draws attention to the nonspecificity of sarcoid tissue and "Schaumann bodies" as evidenced by the production of these features in animals as a hypersensitivity reaction to a non-microbial antigen. According to Refsum, the ob-

tainment of a Kveim reaction, to be described later, indicates that in genuine sarcoidosis one is dealing with only one causative agent or a group of closely related agents.

DIAGNOSIS

Sarcoidosis comes into consideration in the differential diagnosis of practically every obscure disease to which the body may fall heir, including such heterogeneous conditions as ocular lesions, diaphanosis, cardiac disease, portal hypertension, pyloric stenosis and migratory polyarthritis. The following remarks deal in a general way with the diagnosis of systemic sarcoidosis but more specifically with the intrathoracic manifestations. Additional features relating to the latter will be described in relation to the several forms of the pulmonary disease. It should be stated at the outset that inasmuch as the etiology of sarcoidosis is unknown, the diagnosis rests on indirect evidence, chiefly on the demonstration of sarcoid structures in lymph node, liver, bone marrow or other organs and on certain clinical, roentgenological and immunologic features to be discussed presently. A diagnosis of sarcoidosis is made, not only on the basis of positive histological findings, but also by excluding conditions such as those mentioned previously which may produce sarcoid like granulomas. The diagnosis of sarcoidosis rests on a composite of findings rather than on results of individual tests.

Symptoms and Signs

In spite of a multiplicity of organ involvement, the symptoms and signs of systemic sarcoidosis seldom reflect the extent of the disease. This applies especially to any pulmonary involvement which may be present. Massive sarcoidosis may affect the mediastinal lymph nodes and pulmonary parenchyma without causing any localizing symptoms or signs. Low grade fever, malaise, weakness and loss of weight are often encountered. On physical examination one may find enlarged peripheral lymph nodes, splenomegaly and skin lesions but often these are lacking. Several syndromes of sarcoidosis present distinguishing composite features.

Heerfordt's disease or uveoparotid fever is characterized by inflammatory lesions of the uveal tract of the eye painless swelling of the parotid glands and prolonged low grade relapsing fever. Uveoparotitis is probably a variety of Mikulicz syndrome to be discussed later both manifestations of systemic sarcoidosis. In the years prior to the recognition of Boeck's sarcoid as a systemic disease and before the widespread use of chest x-rays only the visible lesions of sarcoidosis were recognized and a tuberculous etiology of the disease seemed quite plausible. In recent years however the frequent demonstration of accompanying pulmonary and hilar lymph node involvement the absence of caseation and the failure to demonstrate tubercle bacilli in the lesions as well as other stigmata of sarcoidosis have served to relegate tuberculosis to the background. The incidence of ocular sarcoidosis depends largely on the material studied. Woods and Guyton ophthalmologists estimate that somewhere between 5 and 10 per cent of uveitis is due to sarcoid and that almost 50 per cent of sarcoid patients show ocular lesions. Systemic sarcoidosis with major involvement in the lungs and hilar lymph nodes is only occasionally associated with ocular lesions.

In 1941 Williams investigated forty cases of chronic iridocyclitis. In twenty-four chest positive x-rays were obtained including twelve cases with diffuse hilar and reticular pulmonary changes two with massive mediastinal and hilar lymph node enlargement without pulmonary changes six with active chronic pulmonary tuberculosis and four with old healed fibrotic or calcific presumably tuberculous pulmonary foci. Williams noted that although the extent of the pulmonary lesions in the patients with active pulmonary tuberculosis was considerable the general condition of the patients was surprisingly good. Although Williams refers to my study on chronic hematogenous tuberculosis in the adult published in 1939 to help support his thesis that his cases were examples of chronic hilar tuberculosis I must confess that my conclusions were incorrect and that much of the material in my study and probably most of the cases cited by Williams represented systemic sarcoidosis.

Mikulicz syndrome is characterized by symmetrical enlargement of the salivary and lacrimal glands. Mikulicz concluded that the tissue changes represented those of a lymphosarcoma. The symptom complex may be due to a distinct disease without associated lesions or it may occur as a syndrome in association with lymphosarcoma leukemia lead and other toxic agents as well as in sarcoidosis with uveal tract involvement.

Case 26 Female—Age 21

The patient gravida 3 para 2 registered at the Morrisania City Hospital Prenatal Clinic in the second month of her pregnancy. A routine prenatal chest x-ray on August 3 1948 in the third month of her pregnancy revealed bilateral hilar lymph node enlargement. The patient was asked to return for further study but by the time she appeared two months later she had developed painless swellings of the parotid and lacrimal glands (Figure 40A).

On admission to the hospital the physical examination disclosed a well nourished female in no obvious discomfort. Both parotid glands were swollen the left larger than the right. The lacrimal glands were enlarged but not tender. There was no palpable adenopathy anywhere else in the body. The breasts were soft and contained no masses. The lungs were clear to percussion and auscultation. The heart revealed nothing abnormal. The liver and spleen could not be felt. The skin over the extensor surface of both legs were studded with lichenoid papules pinkish in color. Neurological examination showed a mild right facial weakness and left trigeminal hypalgesia.

Repeated x-rays of the chest revealed the same degree of enlargement of the hilar lymph nodes as noted in the initial film (Figure 40B). Roentgenograms of the hands and feet sella turcica and Stenson's duct revealed no abnormalities. Numerous examinations of the sputum failed to reveal acid fast organisms. The patient did not react to tuberculin in concentrations up to 10 mg intracutaneously. The results of some of the other laboratory examinations were as follows: Electrocardiogram of the heart was within normal limits. Mazzini was negative. The urinalysis was normal. The white blood cell count was 4900 per cu mm with 64 per cent polymorphonuclear cells 3 per cent lymphocytes and 4 per cent monocytes. The

red blood cell count was 3 720 000 and hemoglobin was 11 gm FSR—18 millimeters in thirty minutes. Total protein was 5.2 gm albumin 4.1 globulin 1.1, calcium 9.6 mg, phosphorus 2.5 mg and alkaline phosphatase 4.1 KA units. Uric acid was 2.3 mg and urea nitrogen was 7 mg per cc. Cholesterol was 363 mg per 100 cc and esters 168.

An aspiration biopsy of the right parotid gland showed round cell infiltration on microscopic examination. A skin biopsy of one of the papules showed some areas in the corium suggestive of epithelioid tubercles but there were not sufficiently characteristic to make a precise diagnosis. The patient remained afebrile and asymptomatic. After a stay of five weeks at the hospital she was discharged and followed in the Chest and Prenatal Clinics. By January 1949 the swelling of the parotid glands had decreased considerably but the condition of the lacrimal glands remained unchanged.

On February 5 1949 the patient was admitted to the hospital in active labor. A transverse presentation was encountered. The fetal heart was good but disappeared as labor progressed. A version and extraction of a stillborn male child was done. Autopsy of the fetus revealed atelectasis of both lungs cerebral edema and minute cerebral hemorrhages. The diagnosis was asphyxiation. There was no evidence of sarcoidosis or tuberculosis. The mother's postpartum course was uneventful.

In March 1949 the patient returned to the Chest Clinic complaining of pain in the left breast. Examination

revealed a plum sized mass in the left upper quadrant. A biopsy of this mass showed hyperplastic breast acini and ducts with many small tubercles consisting of epithelioid cells connective tissue and giant cells but no caseation. The diagnosis was sarcoidosis. Follow-up examinations revealed no significant changes in the chest x-ray findings. The swelling of the parotid glands in time subsided but the right lacrimal gland enlargement was still present when the patient was last seen.

It may be pertinent, at this point, to cite another experience with sarcoidosis complicated by pregnancy with a happier outcome. A Negro woman of twenty-three had given birth to a healthy child at the Morrisania City Hospital five months previously. As a result of a routine chest x-ray taken elsewhere, the patient was referred to the Chest Clinic with a diagnosis of bilateral tuberculosis. The patient had practically no symptoms or signs referable to the chest. Chest x-ray revealed nodular and reticular infiltrations throughout both lungs (Figure 43A). A palpable lymph node was found in the left epitrochlear region which was excised and histologic examination showed many epithelioid tubercles containing occasional Langhans giant cells with a surrounding zone of lymphocytes. There was no caseation. The diagnosis was sarcoidosis. Repeated examination of the sputum failed to reveal



Figure 40 Case 26 Sarcoidosis associated with Mikulicz syndrome. A (Left) Enlarged parotid glands swelling of right lacrimal gland. B (Right) Chest x-ray (early in pregnancy) shows bilateral prominent hilar densities. (Biopsy of breast tissue nodule also of skin revealed changes consistent with sarcoidosis still born at term.)

acid fast bacilli. The tuberculin reaction was negative in concentrations up to 10 mg. The patient was allowed to go to term and delivered a healthy child. Two years later, the patient delivered another healthy infant. In the meantime, the disease in the lungs had undergone spontaneous regression (Figure 43B). A report of this and the preceding case, by Aykan and Jusko witz in 1950, was the first one published on the association of sarcoidosis and pregnancy. I have since followed the course of a third patient with sarcoidosis who went through pregnancy successfully.

Jungling's disease is characterized by cystic changes in small bones which appear roentgenologically as circumscribed areas of rarefaction or, more often, as a reticulated or "lace like" pattern or a combination of both. The phalanges, metacarpals and metatarsals are most often involved, but the nasal bones, humerus, ulna, femur and tibia may also be affected (Figure 41B). There is usually little, if any, joint involvement so that in spite of advanced degrees of bone destruction, the motion of the parts is maintained. With few exceptions, the cystic changes in the small bones are found in association with stigmata of sarcoidosis in other parts of the body. Sarcoidosis of small bones has to be differentiated from multiple cystic tuberculosis, an extremely rare occurrence. The earlier literature on the subject assumed the osseous changes to be caused by the tubercle bacillus, hence the term originally applied by Jungling to this syndrome, "ostitis tuberculosa multiplex cystica."

If one reviews the reported cases of Jungling's disease, one is impressed with the considerable number of children who had negative tuberculin skin reactions and negative guinea pig inoculations. The hilar adenopathy ascribed to childhood tuberculosis was due in most instances to sarcoidosis. Holt and Owens credit Kienbock with the first description of the bone lesions of sarcoidosis, published in 1902. Jungling was among the first to establish histologic proof that the lesions in the bones were due to a granulomatous process identical microscopically to the changes described by Boeck. Of sixty-five patients with generalized sarcoidosis reported by

Holt and Owens, only eleven, or 16 per cent, had definite bone lesions. An almost identical percentage (17.4) of bone lesions was found by Ricker and Clark. Significantly, higher percentages of osseous lesions have been reported from European countries.

A *Banti like syndrome* may be encountered on rare occasions when systemic sarcoidosis is associated with massive enlargement of the liver and spleen and an accompanying ascites. Several reports are on record of patients in whom splenectomy was done in the mistaken belief that the condition was Banti's syndrome. Nordland and co-workers reported the case of a twenty-six year old pregnant woman with thrombocytopenic purpura. Splenectomy was successfully performed in the fifth month of pregnancy. Examination of the extirpated spleen showed sarcoidosis. The pregnancy terminated normally at term. It should be mentioned that Banti's syndrome is such an ill-defined entity that sarcoidosis or any other disease of the liver associated with anemia, leukopenia, splenomegaly and portal hypertension is included in the syndrome. Mino and co-workers reported a case of manifest systemic sarcoidosis with marked hepatosplenomegaly and ascites. After splenectomy and spleno-renal venous anastomosis, the patient experienced considerable symptomatic relief of the ascites, dyspnea and abdominal discomfort. An analogous experience was cited by Dunlap and co-workers. These investigators reported the case of a pregnant woman with portal hypertension that was apparently produced by sarcoidosis involving the liver and spleen. The patient underwent splenectomy, an end to side spleno-renal shunt and five and one half months later delivered a normal baby at home.

Case 27. Female.—Age 36

A colored female was admitted to a hospital complaining of cough, fever, weakness, shortness of breath and loss of twenty-five pounds in weight. More recently, the patient had noted swelling and pain of the abdomen, nausea and vomiting after meals. The immediate cause of the patient's seeking hospital treatment was bleeding from the gums. This had lasted seven hours. The past personal and family histories were irrelevant except for the fact

that two years previously the patient had a seizure of painful swelling of joints and fever. The condition was diagnosed as rheumatic fever and the patient was hospitalized for twenty-five days. On the basis of the chest x-ray findings also a biopsy of an epitrochlear lymph node a diagnosis of tuberculosis was made and the patient was treated with streptomycin and isoniazid for a period of twenty-five days until she was transferred to Seton Hospital.

At Seton Hospital it was soon apparent that one was dealing with systemic sarcoidosis. The chest x-rays revealed bilateral hilar lymph node enlargement and fine reticular striations extending into the midportions of both lungs (Figure 41A). In addition the left scapula showed a punched out cystic area. Repeated examinations of the sputum and gastric contents failed to reveal acid fast organisms. The tuberculin reaction was negative in all strengths. A review of the biopsy of the epitrochlear lymph node revealed noncaseating epithelioid

tubercles with Langhans giant cells some of which contained asteroid inclusion bodies. Of particular interest from the viewpoint of the present discussion was the finding of an enlarged liver which was palpable four fingerbreadths below the right costal margin also a greatly enlarged spleen which occupied the entire left upper quadrant. The presence of secondary anemia and other laboratory tests were in keeping with a Banti-like syndrome due to sarcoidosis.

Tuberculin Reaction

Approximately two thirds of patients with sarcoidosis fail to react to tuberculin or react weakly to concentrations as high as 10 mg. or more. Several theories have been proposed in explanation. Physicians who do not subscribe to the belief that sarcoidosis is causally related to tuberculosis, and these are in the majority, draw the obvious conclusion that a negative tuberculin

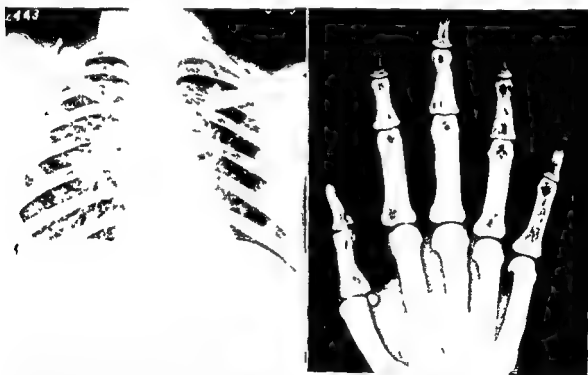


Figure 41 (Case 27) Sarcoidosis associated with a Banti-like syndrome. A (Left) Enlarged hilar lymph nodes, irregular reticular infiltrations permeating both lung fields, cystic area in left scapula. (Biopsy of lymph node revealed changes consistent with sarcoidosis.)

Sarcoidosis associated with Jurgens' disease. B (Right) Phalanges show circumscribed areas of rarefaction (in a patient with proved systemic sarcoidosis).

speaks against tuberculosis. On the other hand those who believe that sarcoidosis and tuberculosis are different facets of the same disease ascribe the lack of reactivity to tuberculin to positive anergy—a questionable state.

In the differential diagnosis a negative tuberculin test is of considerable value providing it is in keeping with other clinical and laboratory findings. It is well known that in moribund states and during intercurrent illnesses the tuberculin reaction may be depressed. This applies also to Hodgkin's disease and mycosis fungoides. As a matter of interest rather than one which sheds any light on the subject it may be mentioned that Lemming was able to produce cutaneous sarcoid lesions by injecting BCG vaccine in a patient with sarcoidosis. Billings and Shipiro document the case of a white female with papular skin lesions of a typically sarcoidlike nature. A biopsy specimen was obtained and at the same time old tuberculin 0.01 mgm. was injected in another site. A positive tuberculin skin reaction was obtained. Approximately a month later another biopsy of a similar papular lesion as well as one taken from the site of the tuberculin injection revealed sarcoidlike lesions in both. Obviously there are many unexplained phenomena associated with sarcoidosis.

Michiel and co-workers found a significantly higher prevalence of tuberculin nonreactors in sarcoidosis in rural areas where negative tuberculin are commonly encountered. These investigators believe that possibly the etiologic agent of the disease may be more heavily concentrated in these areas. It may also explain the higher percentage of sarcoidosis in Negroes born in the Southern rural regions of the United States. But the waxing and waning of the tuberculin skin reaction as may be encountered in sarcoidosis indicates a more profound disturbance. Furthermore the allergic state as expressed in the skin and represented in the tuberculin reaction does not necessarily reflect the allergic state of other organs or the body. In a study of BCG vaccination in twenty patients with sarcoidosis Israel and co-workers found that sarcoidosis patients were unable to develop and maintain skin sensitivity to tuberculin.

The tuberculin anergy in patients with sarcoidosis appears to be nonspecific due to interference with general immunologic mechanisms and does not establish sarcoidosis as an anergic form of tuberculosis. In keeping with this concept Friou found that patients with sarcoidosis showed a depression of activity to extracts of mumps virus, *Candida albicans* and *Trichophyton gypsum*. This depression was greatest in sarcoid patients with negative tuberculin reactions. The results of these tests seem to fit with the belief that sarcoid patients suppress delayed cutaneous reactions to all antigens. Sones and Israel also found that patients with sarcoidosis react significantly less often than do controls to tuberculin, pertussis agglutinin, mumps virus and Oidiomycin. Hence they conclude the relative anergy to tuberculin accompanying sarcoidosis is nonspecific.

Laboratory Findings

There are few adequate studies available of the blood chemistry of large groups of patients with sarcoidosis during the prolonged course of the illness. Some of the reported results based on studies of small numbers of patients are even contradictory, possibly because single examinations are made of different forms or stages of the disease. It may be stated categorically that if laboratory findings are in keeping with the clinical findings they are helpful in diagnosis; in themselves laboratory tests are of little value.

As might be expected of a disease with a predilection for the reticuloendothelial system active sarcoidosis is associated with an elevation of the globulin fraction of the blood chiefly of the gamma fraction with a resulting increase in the total serum proteins. A reversed A/G ratio may be present even if the total serum proteins are within normal limits as is often the case. With subsidence of active disease the A/G ratio tends to return to normal values although the A/G ratio and the clinical activity do not necessarily parallel. Since there are comparatively few conditions (lymphopathia venereum, lupus erythematosus, certain liver diseases, multiple myeloma and Kala Azar) which are characterized by a reversal of the A/G ratio its occurrence in sar-

coidosis is of diagnostic value. The diagnostic significance of other blood chemical values is debatable.

There is often an elevated serum calcium and usually a normal serum phosphorus unless there are associated renal lesions. The alkaline serum phosphatase may also be raised if there is significant liver damage; more often it is within normal limits. In the presence of hypercalcemia one may find nephrocalcinosis and/or nephrolithiasis also soft tissue calcifications. The calcified foci may be present in the sarcoid lesions; more often they are metastatic and not associated with bone disease. Klatzkin and Gordon described two cases of sarcoidosis with hypercalcemia, metastatic calcification in one and renal stones in the other, both associated with renal failure.

A number of investigators have pointed out that sarcoidosis with hypercalcemia and associated metastatic calcification may be mistaken for hyperparathyroidism. Distinguishing features of hyperparathyroidism are found in the generalized decalcification of bones rather than in the localized foci of sarcoidosis. The raised alkaline phosphatase and the normal or low serum proteins are also in keeping with the former. The calcium and phosphorus levels are not dependable in differential diagnosis. It is well to point out that in spite of the frequent involvement of the kidneys with sarcoidosis, renal failure is rare. I encountered one such case but at autopsy the cause of the azotemia and renal failure was found to be due to a polycystic kidney with double ureters and minimal sarcoid involvement.

The blood cytology in sarcoidosis is not distinctive. The erythrocyte sedimentation velocity is increased during the active phase and may or may not approach normal values with subsidence of the disease. The leukocyte count is often within normal range at times slightly above or occasionally below normal except during intercurrent febrile episodes when a leukocytosis is usually present. Although a moderate degree of eosinophilia is common, its absence is of little diagnostic value.

Tissue Examination

Histologic study of tissues of patients sus-

pected of having sarcoidosis is an important feature in the diagnosis of the disease. But as mentioned, the mere demonstration of sarcoid-like granulomas is not sufficient to diagnose systemic sarcoidosis unless confirmed by clinical and roentgenological findings. In fact, a presumptive diagnosis of sarcoidosis can be made with a reasonable degree of accuracy on the basis of significant clinical and roentgenological findings even if a confirmatory biopsy is not available. The most likely sites for the obtainment of biopsy specimens are the skin, lymph nodes and liver. An epitrochlear lymph node is frequently available for biopsy. Other organs and tissues which may be used for biopsy are the uveal tract, salivary glands, tonsils and bone marrow. It may be advisable at times to explore surgically, the root of the neck on the right side to obtain lymph tissue in the paratracheal region; occasionally one may have to resort to a biopsy of lung tissue. The concluding section deals at greater length with the place of biopsies in the differential diagnosis of sarcoidosis and other obscure systemic diseases with pulmonary lesions.

In the absence of easily available tissue, needle biopsy of the liver, an organ frequently involved in sarcoidosis, is an additional means of obtaining material for histological study. Before liver puncture is done, the bleeding coagulation and prothrombin time are tested and other precautions taken. Van Buchem performed liver biopsies on fourteen patients with sarcoidosis. In eleven a positive biopsy was obtained. Of three with negative biopsies, two had arrested disease and the third, typical skin lesions. Klatzkin and Yesner performed liver biopsies in twenty cases of sarcoidosis. They were able to demonstrate submiliary granulomata in fifteen histologically confirmed cases but in none of five with only a presumptive diagnosis. In ten of the former, the histological confirmation of the diagnosis rested on the liver biopsy findings alone. These investigators point out that submiliary granulomata in the liver are also demonstrable by needle biopsy in miliary, pulmonary and osseous tuberculosis, in erythema nodosum and in brucellosis. Smaller, somewhat atypical granulomata are demonstrable in infectious mononucleosis, influenza B, in

certain infections and in actinomycosis. The authors cite others who found such granulomata in early syphilis, leprosy, tularemia and mycotic infections.

Kveim Reaction

An intracutaneous injection of saline suspension of lymph node or other tissue obtained from a patient with active sarcoidosis produces a nodule in certain recipients which on histological examination duplicates closely the structure of the sarcoid tubercle. Originally described by Williams and Nielson in 1935, the test was reintroduced and popularized by Kveim in 1941. The latter, unlike his predecessors, recognized the fact that it is a delayed reaction and that it takes several weeks, often several months, for sarcoid-like tubercles to develop. Lesions developing at the site of injection and showing typical papules have been reported as positive Kveim reactions as late as one to five years after injection. The Kveim reaction is specific insofar as patients with active sarcoidosis, with few exceptions, develop sarcoid-like tubercles. But the test is not a specific one since it may follow intracutaneous injection of suspensions of normal human spleen killed as well as living tubercle bacilli, silica containing material and other substances. Dornbush considers the Kveim reaction an allergic phenomenon; suspensions of sarcoid tissue presumably containing unknown specific substances which are responsible for the development of the skin reaction. There are a number of reasons, however, why the Kveim test cannot be considered an allergic reaction: one being the long latent period which may elapse before a positive test is obtained.

As mentioned, the Kveim reaction is associated with a high percentage of positive results in patients with active sarcoidosis but in a small percentage false positive reactions are also obtained. Sitzbach and Ehrlich performed 571 Kveim tests in 200 patients. A positive reaction, characterized by the production of tubercloid granulomas resembling those of sarcoidosis, was obtained in 86 per cent of patients with biopsy confirmed sarcoidosis. False positive results were obtained in only 4 per cent. It should be noted, however, that among a comparable group of patients

strongly suspected of having sarcoidosis on clinical grounds alone and without biopsy confirmation, the authors also obtained positive Kveim tests in 85 per cent. In other words, the Kveim reaction is not essential for making a diagnosis. In fact, Israel and Sones obtained positive Kveim tests in 42.4 per cent of thirty-three patients with tuberculosis and in 8.3 per cent of other control subjects. Surprisingly, they obtained positive Kveim tests in only 7.1 per cent of patients with sarcoidosis. Contrary to the experience of most investigators, Israel and Sones were unable to confirm the diagnostic value of the Kveim test.

Rogers and Haserel tested 103 patients with Kveim antigen. Of fifty-one patients with clinically active sarcoidosis, only two had negative tests. Six patients with sarcoidosis in clinical remission also gave negative tests. A control group of forty-two patients with other diseases including tuberculosis and berylliosis also gave negative tests. These investigators studied the pathogenesis of the positive Kveim test by comparing positive tests of the same and different durations and by serial biopsy. They concluded that the test is both reliable and practical in the diagnosis of sarcoidosis. They suspect that the disease involves an antigen-antibody mechanism produced by a tubercloid stimulating agent.

A unique experience is cited by Rogers and Netherton of identical twins who developed sarcoidosis. In addition to other similarities, it was noted that in one patient the growth of the papule at the site of injection of the Kveim antigen seemed to parallel the clinical course of the disease. After decreasing in size, coincident with the clinical and chest x-ray findings, the papule grew in size with recurrence of the disease. The lesion was excised about two and one-half years after the initial injection of the Kveim antigen and on histological examination the tissue revealed characteristic focal collections of epithelioid cells and giant cells typical of sarcoidosis. There is still much to be learned about sarcoidosis.

INTRATHORACIC SARCOIDOSIS

Clinical Features

Sarcoidosis of the lungs and hilar lymph nodes

is accompanied by so few symptoms that patients seldom seek medical attention because of complaints referable to the chest. If symptoms relating to the litter are present, they are apt to be caused by incidental factors rather than by the disease per se. Considerable cough and expectoration, occasionally hemoptysis and fever, herald superimposed infection. Increasing dyspnea, orthopnea and edema indicate the development of chronic cor pulmonale.

More often the physician is consulted because of the patient's general malaise and recurring fever or because of gross involvements of the skin, eyes, salivary glands or because of visibly enlarged lymph nodes. In many, sarcoidosis is discovered in the course of routine chest x-ray examinations. Schonholzer, in a chest x-ray survey of 516,879 Swiss soldiers, found sixty-seven cases of pulmonary sarcoidosis, an incidence of 0.13 per cent. The incidence of pulmonary involvement in systemic sarcoidosis varies according to the nature of the material studied and the particular interests of the examiner. Ricker and Clark found evidence of pulmonary involvement in 36 per cent of 300 cases of sarcoidosis proved histologically by biopsy or autopsy. Fisher (quoted by Woods) found pulmonary or mediastinal lymph node involvement in 83 per cent of 94 carefully studied cases.

Roentgenology

Intrathoracic sarcoidosis presents roentgenologically such diversified appearances that the differential diagnosis takes in a large number of diseases which may affect the lungs and/or hilar lymph nodes. From a study of a sizable number of cases of sarcoidosis, one may distinguish three broad roentgenologic patterns of the disease, one often merging with the other.

A *bilar* form is characterized by bilateral hilar lymph node enlargement (Figure 40B). At times (Figure 45B), the tumefactions are massive and assume a "potato"-like configuration. At this stage, the disease is apt to be mistaken for a malignant lymphoma. It is not improbable that of the histologically unproved cases of Hodgkin's disease or lymphosarcoma "cured" by one means or another, many represent spontaneously

regressing sarcoidosis of the hilar lymph nodes.

A *transitional* form, consisting of enlarged hilar lymph nodes plus parenchymal involvement, is probably the most frequent one encountered (Figure 41A). At this stage, sarcoidosis may simulate lymphangitic carcinomatosis, pneumoconiosis as well as malignant lymphomas.

A *parenchymal* form of the disease, usually but not necessarily associated with some degree of hilar lymphadenopathy, may assume an appearance of miliary nodules (Figures 42A and B), reticular striations (Figure 43A), diffuse interstitial fibrosis, focal fibrosis and emphysema (Figures 44A and B) or scattered rounded densities. The differential diagnosis includes tuberculosis, fungus infections, dust inhalational diseases, berilliosis, lymphangitic carcinomatosis and metastatic neoplasms, among a number of other conditions.

Intrathoracic sarcoidosis often undergoes spontaneous resolution, as far as can be judged roentgenologically, but the exact incidence of this outcome has not been established (Figures 45A, B and C). Spontaneous regression may take a few weeks or several years. In a variable number, sarcoidosis, after developing to a certain stage, becomes arrested and, in time, assumes the picture of a diffusely fibrosing disease with emphysema. Examination of such a lung may not provide any histologic evidence of sarcoidosis although the initial phases of the disease may have been featured by classical symptoms, signs and laboratory findings. The disease may remain in a stage of arrest for many years. Dinolt described the findings in the first case of the disease reported by Boeck forty-one years earlier.

In a certain percentage of cases the disease, usually in the advanced stages is complicated by superimposed tuberculosis. A pleural effusion may then make its appearance. Uncomplicated intrathoracic sarcoidosis is rarely associated with a pleural effusion, rather unusual of a disease which is believed to be allergic in nature. Sarcoidosis of the lungs, associated with progressive fibrosis and emphysema, by causing increasing interference with the lesser circulation, leads in some cases to chronic cor pulmonale. A coexist-



Figure 42 Sarcoidosis miliary type A (Upper left) Minute infiltrations involving both lungs B (Upper right) Detail showing foci and reticulations (Disease discovered accidentally chest x rays unchanged over a period of eight years no symptoms or signs referable to chest biopsy of lymph node tuberculin and other tests in keeping with sarcoidosis)

Figure 43 Sarcoidosis nodular type A (Lower left) Nodular and reticular infiltrations seeding both lungs enlarged right paratracheal lymph nodes (Biopsy of lymph node revealed tissue changes consistent with sarcoidosis) B (Lower right) Four years later clearing of infiltrations and regression of paratracheal lymph nodes. (In the interim patient bore two healthy children)



Figure 44. Sarcoidosis parenchymal form. A (Left) Irregular, dense infiltrations in both upper lobes apical and basal regions hyperillumination (Admitted to sanatorium with diagnosis of pulmonary tuberculosis). B (Right) Nine years later marked fibrosis of upper lobes and emphysema of remainder (Biopsy of lymph node early in disease revealed sarcoidosis died of chronic cor pulmonale autopsy showed intense fibrosis and nodularity of lungs no evidence of caseation no acid fast bacilli in tissues hypertrophy of right ventricle).

ing sarcoidosis of the heart may be a contributing factor

TREATMENT

There is no specific remedy for sarcoidosis because the etiology of the condition is unknown and the effects of treatment cannot be assessed since the disease is often self limited. Among the many therapeutic measures which have been utilized a combination of streptomycin and cortisone appears most promising at the time of this writing.

Streptomycin was initially used alone on the premise that sarcoidosis may represent an atypical form of tuberculosis. But the results were not impressive excepting in cases with manifest tuberculosis complicating sarcoidosis. Following observations on the effect of ACTH on certain inflammatory diseases of the eyes, Sones and co-workers tested the effect of cortisone in two cases of widespread sarcoidosis. The administration of cortisone, in doses of 100 mgs twice daily, was

followed by marked amelioration of symptoms. The clinical improvement was paralleled by changes in the tissues obtained by biopsy after treatment. The regression of the disease appeared to be at a faster rate than that observed in cases undergoing spontaneous healing.

Subsequent reports by Lovelock and Stone, Small and others confirmed the immediate beneficial effects of cortisone on sarcoidosis, serial chest x-rays showing not only decided clearing of the pulmonary lesions but improvement in function as well. Somewhat disappointing results were obtained by Michael in ten patients with sarcoidosis treated with cortisone. Like others he found cortisone to cause amelioration of symptoms but this did not seem to alter the basic course of the disease. After the discontinuance of medication the lesions resumed their original state. This phenomenon has since been confirmed by others (Figures 46 A, B, C and D). Furthermore, in one instance reported by Small where a patient had received cortisone daily for

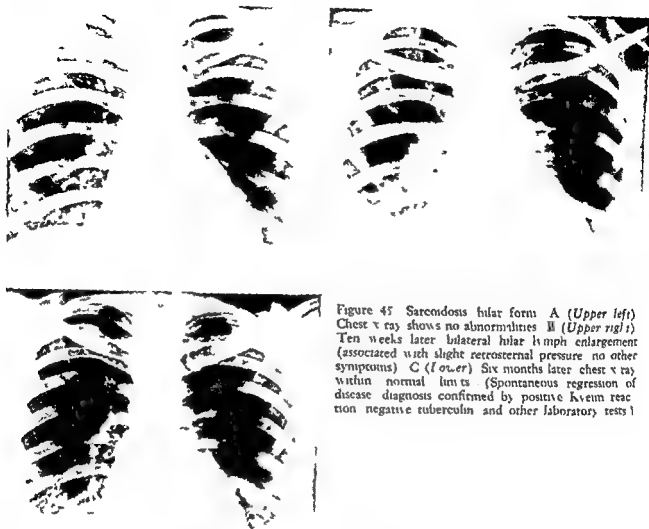


Figure 45 Sarcoidosis hilar form. A (Upper left) Chest x ray shows no abnormalities. B (Upper right) Ten weeks later bilateral hilar lymph enlargement (associated with slight retrosternal pressure, no other symptoms). C (Lower left) Six months later chest x ray within normal limits. (Spontaneous regression of disease, diagnosis confirmed by positive Kveim reaction, negative tuberculin and other laboratory tests).

forty-five days tuberculosis developed in the spine and urogenital tract. The hazard of the administration of ACTH and cortisone to patients with latent tuberculosis is now recognized. Controlled studies on the experimental animal parallel the observations in man.

Israel and co-workers recently reported their experience with thirty-six cases of sarcoidosis treated with cortisone. They found that benefit was most striking in patients with extrapulmonary lesions in the eyes, parotid glands, skin, or heart and most marked in patients with recent disease. However, improvement in the pulmonary lesions was less frequently observed and no

effect was noted on mediastinal lymphadenopathy. Definite improvement occurred in 50 per cent of patients with pulmonary infiltrations; in a few instances there was complete resolution. These investigators did not encounter any instances of tuberculosis. The failure to observe febrile relapses during or after cortisone treatment seemed sufficiently impressive to lead these investigators to conclude that sarcoidosis was probably not caused by an infectious agent. Four patients died of progressive sarcoidosis who could not tolerate discontinuance of therapy.

Hoyle and co-workers analyzed the reported results of treatment of pulmonary sarcoidosis

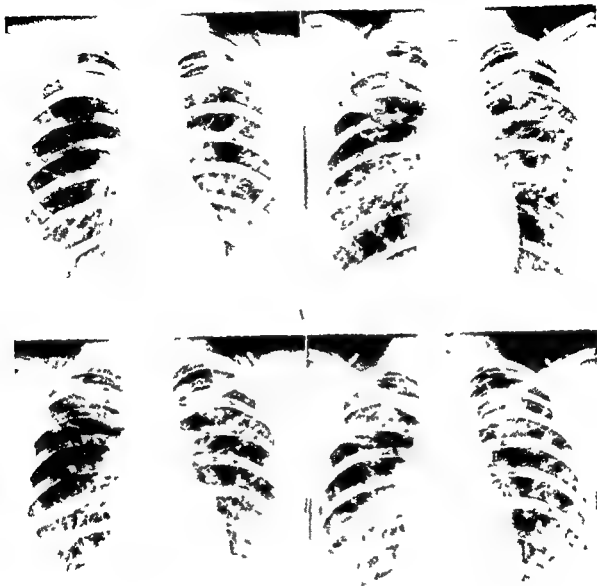


Figure 46 Sarcoidosis temporary improvement under cortisone treatment. A (Upper left) Faint reticular infiltrations more marked in left lung. B (Upper right) Five years later patchy infiltrations involving both lungs (suggesting metastatic neoplasm). C (Lower left) After four months cortisone treatment moderate degree of regression of infiltrations. D (Lower right) Five months after discontinuance of cortisone infiltrations more extensive than before treatment. (Course of disease featured by a minimum of symptoms and physical signs. Regression of steroid treatment was again followed by regression of infiltrations.)

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE

with cortisone or ACTH. On the basis of a radiological assessment of eighty nine cases, sixty-five showed improvement after three months of treatment. However, partial relapse occurred in eleven and complete relapse in twenty six. The percentage of those who maintained their improvement corresponds roughly with that obtained by Israel and co workers. On the basis of an original study of thirty eight patients with pulmonary sarcoidosis, of which thirty were treated with streptomycin plus para-aminosalicylic acid (PAS) and with cortisone plus streptomycin and PAS. Hovle and co workers found that the latter combination was much superior. They also noted that the improvement was more

frequent and more complete among the patients with recent disease. They found it safe to combine the treatment up to a year. Unfortunately, it was difficult to decide when the treatment should be given, as many others have found and when it should be stopped. One must conclude, therefore, that although a trial of cortisone or ACTH, preferably in combination with streptomycin and PAS, is indicated in acute forms of sarcoidosis, the benefit to be derived from treatment of chronic forms of the disease, especially sarcoidosis of the lungs, is problematic. In any event, one has to be on guard against untoward reactions which may arise as a result of sudden withdrawal of the hormone.

Bibliography

- ARBELE, D. and MADONICK, M. Uveo parotid Fever (Heerfordt's Syndrome) Neurologic Manifestations *Am J M Sc* 196 222 1938
- AXMAN, T. and JUSKOWITZ, N. Sarcoidosis and Pregnancy *Dis Clini* 17 544 1950
- BILLINGS, G. T. JR. and SHAPIRO, J. L. The Induction of Sarcoid Like Lesions by the Injection of Tuberculin Bull *Johns Hopkins Hosp* 94 139 1954
- BJERREKLEVD, C. J. Boeck's Sarcoid With Erythema Nodosum As An Initial Symptom *Acta med scandinav* 128 538 1947
- BLOCH, R. G. Sarcoidosis *N Clin North America* 37 879 1953
- BOECK, G. Multiple Benign Sarcoid of Skin *J Cutan & Genito Urim Dis* 17 543 1899
- COOVELL, R. H. Sarcoidosis With Special Reference to Diagnosis and Prognosis *Quart J Med*, 23 29 1954
- CLANNINGHAM, J. A. Characteristics of Stellate Inclusions in Giant Cells and the Associated Tissue Reactions *Am J Pathol*, 27 761 1950
- DANBOLT, N. On Kveim's Reaction in Boeck's Sarcoid *Acta med scandinav* 114 143 1943
- DANBOLT, N. Reexamination of Caesar Boeck's First Patient with Multiple Benign Sarcoid of Skin *Scler med Wochschr* 71 1149 1947
- DAVISON, C. N. DENNIS, J. M. MCNIGHT, E. R. WILSON, J. K. V. and BROWN, W. H. Nephrocalcinosis Associated with Sarcoidosis *Radiology* 62 703 1954
- DUNLAP, R. W. JR. HALLENBECK, G. A. and HANCOCK, D. G. Portal Hypertension Associated with Sarcoidosis and with Hemochromatosis. Report of 2 Cases with Splenectomy and Splenorectal Anastomosis *Proc Staff Meet Mayo Clin* 27 766 1952
- ENGLE, R. L., JR. Sarcoid and Sarcoid Like granulomas. A Study of twenty-seven post mortem examinations *Am J Path* 29 53 1953
- FRIEDMAN, D. G. Sarcoidosis *New England J Med* 759 664 1948
- FRIEDMAN, M. Sarcoidosis of Spleen Report of Case with Autopsy and Study of Intracellular "Asteroid Bodies" *Am J Path* 70 671 1944
- FRIOT, G. J. A Study of the Cutaneous Reactions to Oid mycin Trichophyton and Mumps Skin Test Antigen in Patients with Sarcoidosis *Yale J Biol & Med* 24 533 1952
- HEERFORDT, C. F. Über eine Febris uveoparotidea subchronica" an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paräsen cerebrospinaler Nerven kompliziert *Arch Ophth* 70 754 1909
- HOLT, J. F. and OWENS, W. I. The Osseous Lesions of Sarcoidosis *Radiology* 53 11 1949
- HOYLE, C., DAWSON, J. and MATHER, G. Treatment of Pulmonary Sarcoidosis with Streptomycin and Cortisone *Lancet* 1 638 1955
- HUTCHINSON, J. Illustrations of Clinical Surgery London J A Churchill Folio 1875 p 47
- ISRAEL, H. L. DELAMATER, E. SONES, M. WILLIS, W. D., and MARGELSTEIN, A. Chronic Disseminated Histoplasmosis *Am J Med* 12 252, 1957
- ISRAEL, H. L., SONES, M., and HARBELL, D. Cortisone Treatment of Sarcoidosis. Experience with Thirty Six Cases *JAMA* 154 461 1954
- ISRAEL, H. L., SONES, M., STEIN, S. C., and ARONSON, J. D. BCG Vaccination in Sarcoidosis *Am Rev Tuberc*, 62 408 1950
- ISRAEL, H. L., and SONES, M. The Diagnosis of Sarcoidosis with Special Reference to the Kveim Reaction *Ann Int Med* 43 1269 1955
- JUNGUNG, O. Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochen-tuberkulose) *Fortschr Geb Röntgenstrahlen* 7 375 1919 1970
- KERLEY, P. Significance of Radiological Manifestations of Erythema Nodosum *Brit J Radiol*, 11 155 1947
- KLATZMAN, G. and GORDON, V. Renal Complications of Sarcoidosis and their Relationship to Hyperealcemia *Am J Med*, 15 484 1953

with cortisone or ACTH. On the basis of a radiological assessment of eighty-nine cases, sixty-five showed improvement after three months of treatment. However, partial relapse occurred in eleven and complete relapse in twenty-six. The percentage of those who maintained their improvement corresponds roughly with that obtained by Israel and co-workers. On the basis of an original study of thirty-eight patients with pulmonary sarcoidosis, of which thirty were treated with streptomycin plus para-aminosalicylic acid (PAS) and with cortisone plus streptomycin and PAS. Hoyle and co-workers found that the latter combination was much superior. They also noted that the improvement was more

frequent and more complete among the patients with recent disease. They found it safe to combine the treatment up to a year. Unfortunately, it was difficult to decide when the treatment should be given, as many others have found, and when it should be stopped. One must conclude, therefore, that although a trial of cortisone or ACTH, preferably in combination with streptomycin and PAS, is indicated in acute forms of sarcoidosis, the benefit to be derived from treatment of chronic forms of the disease, especially sarcoidosis of the lungs, is problematic. In any event, one has to be on guard against untoward reactions which may arise as a result of sudden withdrawal of the hormone.

Bibliography

SARCOIDOSIS

- ABRUSSE D. and MADONICK M. "Veno parotid Fever (Heerfordt's Syndrome) Neurologic Manifestations." *Ann J M Sc* 196 192 1938.
- AYKAN F. and JUSKOWITZ N. "Sarcoidosis and Pregnancy." *Dis Chest* 17 544 1950.
- BILLINGS F. T. JR. and SHAPIRO J. L. "The Induction of Sarcoid Like Lesions by the Injection of Tuberculin." *Bull Johns Hopkins Hosp* 94 119 1954.
- BJERKELUND C. J. "Boeck's Sarcoid With Erythema Nodosum As An Initial Symptom." *Acta med scandinav* 178 538 1947.
- BLOCH R. G. "Sarcoidosis." *M Clin North America* 37 879 1953.
- BOECK G. "Multiple Benign Sarcoid of Skin." *J Cutan & Genito Urim Dis* 17 543 1899.
- COOVELL R. H. "Sarcoidosis With Special Reference to Diagnosis and Prognosis." *Quart J Med* 23 99 1954.
- CUNNINGHAM J. A. "Characteristics of Stellate Inclusions in Giant Cells and the Associated Tissue Reactions." *Am J Path* 27 761 1950.
- DANBOLT N. "On Kiehm's Reaction in Boeck's Sarcoid." *Acta med scandinav* 114 143 1943.
- DANBOLT N. "Reexamination of Caesar Sarcosis's First Patient with Multiple Benign Sarcoid of Skin." *Seltzer med W chehrer* 77 1149 1947.
- DAVIDSON C. N., DENNIS J. M., MCNACHI E. R., WILSON J. K. V. and BROWN W. H. "Nephrocalcinosis Associated with Sarcoidosis." *Radiology* 67 203 1954.
- DELLAP R. W. JR., HALLENBECK G. A., and HANLON D. G. "Portal Hypertension Associated with Sarcoidosis and with Hemochromatosis. Report of 2 Cases with Splenectomy and Splenoportal Anastomosis." *Proc Staff Meet., Mayo Clin* 27 266 1952.
- ENGLER L. JR. "Sarcoid and Sarcoid Like granulomas. A Study of twenty-seven post mortem examinations." *Am J Path* 29 53 1953.
- FRIEDMAN D. G. "Sarcoidosis." *New England J Med* 239 664 1948.
- FRIEDMAN M. "Sarcoidosis of Spleen. Report of Case with Autopsy and Study of Intracellular Asteroid Bodies." *Am J Path* 20 671 1944.
- FRIOL G. J. "A Study of the Cutaneous Reactions to Old tuberculin, Trichophyton and Mumps Skin Test Antigens in Patients with Sarcoidosis." *Yale J Biol & Med* 24 533 1952.
- HEERFORDT C. F. "Über eine Febris uveoparotidea sub chronica an der Glandula parotis und der Uvea des Auges lokalisiert und häufig mit Paracens cerebrosplanaler Nerven kompliziert." *Arch Ophth* 70 354 1909.
- HOLT J. F. and OWENS W. I. "The Osseous Lesions of Sarcoidosis." *Radiology* 53 11 1949.
- HOYLE C., DAWSON J. and WATHER G. "Treatment of Pulmonary Sarcoidosis with Streptomycin and Cortisone." *Lancet* 1 638 1955.
- HUTCHINSON J. "Illustrations of Clinical Surgery." London J. A. Churchill. Folio 1875 p. 47.
- ISRAEL H. L., DELEXTERER E., SOVES M., WILLES W. D. and KAMELSTEIN A. "Chronic Disseminated Histoplasmosis." *Am J Med* 12 252 1952.
- ISRAEL H. L., SOVES M., and HARRELL D. "Cortisone Treatment of Sarcoidosis. Experience with Thirty Six Cases." *J A M A* 156 461 1954.
- ISRAEL H. L., SOVES M., STEIN S. C. and ARONSON J. D. "BCG Vaccination in Sarcoidosis." *Ann Int Tuberc* 62 408 1950.
- ISRAEL H. L. and SOVES M. "The Diagnosis of Sarcoidosis with Special Reference to the Kiehm Reaction." *Ann Int Med* 43 1269 1955.
- JUNGEL O. "Ostitis tuberculosa multiplex cystica (eine eigenartige Form der Knochentuberkulose)." *Fortschr Geb Röntgenstrahlen* 27 375 1919 1920.
- KERLEY P. "Significance of Radiological Manifestations of Erythema Nodosum." *Brit J Radiol* 15 155 1947.
- KLATSKIN G. and GORDON M. "Renal Complications of Sarcoidosis and Their Relationship to Hypercalcemia." *Am J Med* 15 484 1953.

Pulmonary Manifestations of Certain Abdominal and Metastatic Diseases

Pulmonary Manifestations of Abdominal Diseases

INTRODUCTION

AN ADEQUATE description of the various abdominal conditions which may be associated with pleuropulmonary manifestations would involve a more elaborate discussion of the subject than can be accommodated within the scope of these pages. For the present purposes it will suffice merely to define the more important diseases. It should be stated at the outset that a complete examination of the thoraco-abdominal region as much of it as can be visualized in conventional chest roentgenography utilizes fluoroscopy as well as chest x-rays. The latter include exposures in expiration and inspiration. In obscure disease one has to examine the entire gastrointestinal tract including the use of a barium enema. Occasionally the induction of a pneumoperitoneum is indicated and in particularly difficult situations, exploratory surgery.

Diseases originating in the abdominal cavity may be reflected in the thoracic cavity in one of several ways: (1) by the pressure exerted on the diaphragm and the resulting limitation of motion of the muscle thereby interfering with aeration of the lungs; (2) through localized bulgings of the diaphragm or herniation of abdominal viscera; (3) through the formation of

all is not well below the diaphragm may first be apparent in a chest x-ray.

In the course of routine chest roentgenography of newly admitted patients to general hospitals with a diagnosis of acute surgical abdomen one may find occasionally collections of free air under one or both leaves of the diaphragm. The accidental discovery of escaped air under such circumstances indicates the presence of a perforated abdominal viscus. At other times one may find the diaphragm unduly elevated by gaseous distention of the bowel; the latter possibly showing fluid levels. These findings are in keeping with strangulation of the gut.

Karl Lin and Gilbertson have drawn attention to the importance of inspecting the air-filled upper segment of the stomach in reading chest x-rays. The gas bubble at the cardiac end of the stomach is normally smooth and translucent. A mass projecting into the gas bubble may be clearly visible and the presence of tumor strongly suspected from the routine chest x-ray examination alone (Figures 47A and B). Large neoplasms or infiltrative lesions may cause deformity of the fundus of the stomach or even complete obscuration of the gas bubble.

—DISEASES OF THE DIAPHRAGMATIC REGION

Diaphragmatic Displacements

Diseases of the lungs and mediastinum may interfere with diaphragmatic activity as a result of fixation of the muscle by pleural adhesions or as a result of upward suction of the diaphragm

event the presence of disease in the abdomen may be first evident above the level of the diaphragm and contrariwise the first inkling that

- WILLIAMS E R On the Radiological Aspects of an Investigation into the Relationship of Chronic Indolent Cystitis, Uveo Parotitis and Tuberculosis *Brit J Radiol* 14 116 1941
- WILLIAMS R H and NICKERSON D A Skin Reactions in Sarcoidosis *Proc Soc Exper Biol & Med* 33 403 1935
- WOOLS A C Sarcoidosis The Systemic and Ocular Manifestations *Tr Am Acad Ophth* 333 March April 1949

On rare occasion, the diaphragm may be the site of a tumor originating in the muscle. The neoplasms most frequently encountered are lipomas and fibrosarcomas. Partial eventrations of the right leaf of the diaphragm causing localized bulging of the muscle are often seen (Figure 49A and B). Such circumscribed bulgings almost invariably affect the anteromedial portion of the diaphragm and may simulate tumor. Obvious intraabdominal conditions such as advanced pregnancy, ascites and abnormally enlarged viscera or tumor masses, which may cause diaphragmatic displacement, need only be mentioned.

An intrapulmonary collection of fluid usually an empyema, may simulate an elevated diaphragm or a subphrenic abscess or tumor. If the involvement is on the left side the presence of the stomach bubble or gas containing colon may permit a proper diagnosis. The stomach bubble may be accentuated by a carbonated drink before fluoroscopy. If the fluid is encapsulated beneath the right lung, the differential diagnosis between supra- and infradiaphragmatic disease is much more difficult. Thoracentesis may

be unsuccessful because of the localized nature of the fluid, the encapsulation being caused by adhesions which anchor the lung to the diaphragm. Chest x-rays in lateral decubitus projections may also be unrevealing. Under such conditions, a diagnostic pneumoperitoneum is the best means of demarcating the position of the diaphragm and thereby localizing the fluid collection.

Eventration of the diaphragm is a developmental anomaly of the muscle affecting in most instances, the left leaf (Figure 48B). The highly pliable diaphragm may or may not be associated with Hiernock phenomenon. Eventration should be differentiated from an abnormally elevated stomach due to a congenitally shortened esophagus. In case of the former, after a barium meal the radiopaque mass is visible at a higher plane than that of the esophageal opening. At this juncture, it might be profitable to mention the occasional encounter of pulmonary disease secondary to cardiospasm or mega esophagus. As might be expected the overflow of esophageal contents into the lungs is apt to cause aspiration



Figure 48 A (Left) Paralysis of left leaf of diaphragm caused by a bronchogenic carcinoma invading the phrenic nerve. B (Middle) Paralysis of left leaf of diaphragm caused by a bronchogenic carcinoma invading the laryngeal nerve. C (Right) Paralysis of left leaf of diaphragm caused by a bronchogenic carcinoma invading the recurrent laryngeal nerve. (Note the recurrent laryngeal nerve shadow and dizziness when lying on the left side.)



Figure 47 Carcinoma of stomach discovered accidentally in routine chest x rays. A (Left) Rounded density at cardia of stomach. B (Right) After barium meal mass is seen more clearly. (At operation a carcinoma was found originating at lower end of esophagus protruding into stomach, subtotal gastrectomy and gastroesophagostomy.)

by abnormally high negative intrapleural pressure. Acute peritonitis, pneumoperitoneum, ascites and markedly enlarged abdominal viscera may likewise push the diaphragm upward and interfere with diaphragmatic motion. The activity of the diaphragm may be hindered through actual disease of the muscle or as a result of reflex action initiated elsewhere. It is noteworthy that the pressure immediately beneath the diaphragm fluctuates in the same direction as it does immediately above the muscle. The equalized pressure of the thoraco-abdominal region facilitates the return of blood to the right side of the heart but also acts adversely by aiding the transfer of free fluid and infectious elements through the diaphragm.

Pleuropulmonary fibrosis with shrinkage of the intrathoracic contents is a frequent cause of retraction and upward displacement of the diaphragm. The latter is also brought about by bronchial obstruction and pulmonary atelectasis.

A reduction of activity of the diaphragm may be detected fluoroscopically by having the patient sniff or cough thereby inducing a jerky motion of the muscle. Paralysis of the phrenic nerve by an invading malignant tumor is a common cause of diaphragmatic displacement (Figure 48A). It should be noted that phrenic nerve paralysis due to invading carcinoma need not necessarily be associated with a visible tumor mass. The chest x ray may fail to show any abnormalities aside from the elevated diaphragm. Occasionally both the phrenic and recurrent laryngeal nerves are compromised. Early in the disease, the paralysis may be transient, with continued invasion the paralysis becomes permanent. The highly placed diaphragm is usually associated with a paradoxical motion of the muscle, the latter moving upward in inspiration and downward in expiration (Kienbock phenomenon). Aortic aneurysm may also cause phrenic nerve paralysis.



(See legend on opposite page)



Figure 49 Localized bulging of diaphragm simulating tumor A (Left) Rounded mass immediately above right leaf of the diaphragm B (Right) Lung detail (In the lateral projection the mass was situated anteriorly, to the right of the sternum patient under observation for more than six years without change in configuration of the mass, bronchoscopy and other studies negative for neoplasm)

pneumonia and suppuration (Figures 50A, B C and D) Prolonged low-grade infection results in a chronic nonspecific pneumonitis usually involving the right lower lobe Since mega-esophagus may be associated with few or insignificant symptoms, it is well to bear this condition in mind in the differential diagnosis of any obscure pulmonary disease with features of an aspiration infection

Herniation of the diaphragm may be developmental or acquired usually the former Developmental defects may vary from total absence of the muscle to circumscribed weaknesses which allow limited protrusions of abdominal contents Favorite sites of herniation are in the dorsolateral aspect of the diaphragm through the

foramen of Bochdalek, or through the esophageal hiatus posteriorly or through the foramen of Morgagni, parasternally Hernias are termed false if they have no covering sac, in which case they are apt to allow free passage of multiple abdominal viscera The resulting pressure exerted on the heart and lungs often leads to early death unless the defect is corrected surgically Massive congenital hernias are almost invariably of the false type

Hiatus hernia is a common occurrence in elderly persons The condition often mimics acute coronary artery disease, paravertebral abscess mediastinal collections of fluid or neoplasms O'Connor and Rizzo draw attention to several features which may enable the physician

Figure 50 Mega esophagus complicated by aspiration pneumonia A (Upper left) Widening of superior mediastinum lung clear heart slightly enlarged B (Upper right) Irregular consolidation of right lower lung (associated with chill fever pain in chest and fetid sputum) C and D (Lower left and right) Esophagogram showing markedly dilated esophagus (History of recurring seizures of vomiting and pulmonary infection, partial improvement after passage of mercury weighted tube and antibiotics)

pleura ■ supplied by branches of the internal mammary and intercostal arteries tributaries of the subclavian arteries. As a result inflammatory disease and circulatory disturbances may affect the pleural cavity by way of the greater circulation.

What ■ particularly significant from the viewpoint of the present discussion ■ the fact that a sudden seizure of chest pain and fever the elicitation of a pleural friction rub and the appearance of fluid in the chest may indicate a systemic as well as a local source. As has been repeatedly stressed in these pages involvement of the pleura may be the first manifestation of a systemic disease. In any large collection of pleurisies of diverse origin ■ sizable number remain unexplained. Many of the latter undoubtedly represent manifestations of systemic diseases which never come to light or appear at a later date in more definitive form. A frequent cause

of unexplained pleurisy with effusion in young persons is tuberculosis of the spine. In older persons metastatic malignancy of the spine or of the ribs may be a cause.

Pleurisies of whatever origin are usually associated with free fluid in one or both pleural cavities. Initially it may be difficult to demonstrate a diaphragmatic pleurisy since as has been shown by a number of investigators the pleural cavity has to contain at least 300 cc. of fluid before the collection becomes visible in the chest x-ray. With increasing size the fluid rises above the costophrenic sinus and is demonstrable roentgenologically. The fluid soon rises upward and laterally along the costal margin in time displacing the heart and mediastinum to the contralateral side. At times difficulties may be encountered in diagnosing an acute diaphragmatic pleurisy because the accompanying pain may be referred to the neck or abdomen. In case of the



Figure 52. Pleural effusion as an early sign of metastatic carcinoma. A (Left) Pleural effusion occupying lower half of right chest; heart not displaced; visible parenchyma not involved. B (Right) ■ 3 years later several circumscribed densities are seen in both lungs; pleuritis at right base. (At this time symptoms appeared referable to the abdomen. X-rays of the gastrointestinal tract showed a mass at the rectosigmoid junction. Exploratory laparotomy revealed an inoperable carcinoma of colon.)



Figure 51 Parasternal diaphragmatic hernia A (Left) Rounded edge of a density faintly seen at right cardio-diaphragmatic angle (Note absence of stomach bubble) B (Right) Barium meal shows stomach displaced to the right the barium occupying the density previously noted (In the right lateral projection the herniation was seen to be in the region of the foramen of Morgagni parasternally. The patient a man of thirty had been treated for many years for unexplained anemia)

to suspect the presence of a hiatus in the routine chest x ray. In the posteroanterior projection a small hiatus hernia is superimposed on the heart shadow, slightly to the left of the lateral border of the spine. The hernia appears as a rounded or ovoid shadow, either of a soft appearance if filled with fluid, or as a localized area of hyperillumination if filled with air. In the lateral projection the hernia is found to be in back of the heart. Of particular significance is the absence of the stomach gas bubble in the usual position due to displacement of the organ medially and upward in right-sided parasternal diaphragmatic hernia (Figures 51A and B).

Opaque meal studies are essential to confirm the diagnosis of diaphragmatic hernia. Since the stomach and colon, including omentum, are the most frequent organs displaced, the examination of the barium-filled gastrointestinal tract should include x-ray exposures in the Trendelenburg as well as in conventional positions. Jenkinson and Roberts estimated that only 5 per cent of hiatus

hernias could be diagnosed if the erect position alone were used in the examination. Among 3448 patients examined in a two-year period Brick found 308 hernias of the esophageal hiatus, an incidence of 8.93 per cent. This was the second most frequent lesion diagnosed, duodenal ulcer being found in 20.41 per cent of the patients. Hiatus hernia was more than twice as frequent as gastric ulcer or gastric carcinoma.

Diaphragmatic Pleurisy

A pleurisy may be caused by a variety of agents including bacterial, viral, neoplastic, and traumatic (Figures 52A and B). The pleura may be involved by extension of disease from the lungs, lymph nodes, spine, pericardium, or other structures within the chest, from abdominal organs, and from distant sites. The blood supply of the pleura renders the membrane especially vulnerable to systemic disease. The visceral pleura is supplied by capillaries derived from the bronchial arteries, tributaries of the aorta; the parietal

pleura ■ supplied by branches of the internal mammary and intercostal arteries tributaries of the subclavian arteries. As a result inflammatory disease and circulatory disturbances may affect the pleural cavity by way of the greater circulation.

What ■ particularly significant from the viewpoint of the present discussion is the fact that a sudden seizure of chest pain and fever the elicitation of ■ pleural friction rub and the appearance of fluid in the chest may indicate a systemic as well as a local source. As has been repeatedly stressed in these pages involvement of the pleura may be the first manifestation of a systemic disease. In any large collection of pleuritis of diverse origin a sizable number remain unexplained. Many of the latter undoubtedly represent manifestations of systemic diseases which never come to light or appear at a later date in more definitive form. A frequent cause

of unexplained pleurisy with effusion in young persons is tuberculosis of the spine. In older persons metastatic malignancy of the spine or of the ribs may be a cause.

Pleurisies of whatever origin are usually associated with free fluid in one or both pleural cavities. Initially it may be difficult to demonstrate a diaphragmatic pleurisy since as has been shown by a number of investigators the pleural cavity has to contain at least 300 cc. of fluid before the collection becomes visible in the chest x ray. With increasing size, the fluid rises above the costophrenic sinus and is demonstrable roentgenologically. The fluid soon rises upward and laterally along the costal margin in time displacing the heart and mediastinum to the contralateral side. At times difficulties may be encountered in diagnosing an acute diaphragmatic pleurisy because the accompanying pain may be referred to the neck or abdomen. In case of the



Figure 52. Pleural effusion as an early sign of metastatic carcinoma. A (Left) Pleural effusion occupying lower half of right chest; heart not displaced; visible parenchyma not involved. B (Right) Six years later several circumscribed densities are seen in both lungs; pleuritis at right base. (At this time symptoms appeared referable to the abdomen. X rays of the gastrointestinal tract showed a mass at the rectosigmoid junction; exploratory laparotomy revealed an inoperable carcinoma of colon.)

latter, the symptoms may simulate an acute surgical abdomen'

Subphrenic Abscess

A purulent collection of fluid below the diaphragm seldom originates in the chest but signs of its presence are often first demonstrable above the diaphragm. In the majority of cases a subphrenic abscess results from extension of infection from the abdomen. Infection of the subphrenic spaces is aided by the normally negative pressure in this region, the rich lymphatic supply of the diaphragm favoring the transfer of infection to the pleural surface. A pleural effusion develops early with fixation and elevation of the diaphragm on the affected side. The demonstration of free air or a fluid level under the diaphragm, in a patient who had recently undergone an abdominal operation, points strongly to a subdiaphragmatic abscess.

The chest x-ray is also of inestimable value in the detection of pleuropulmonary complications, following abdominal operations. The incidence of atelectasis pneumonia and pleural effusion is notoriously high after operations on the stomach, duodenum and biliary tract, especially in patients subject to bronchitis, emphysema or other conditions interfering with cough. This applies also to patients who have restrictive abdominal binders or are under excess sedation. The retained secretion in the smaller bronchi causes segmental atelectasis leading to broncho pneumonia. Even in the years when chest roentgenography was done only after the appearance of symptoms pointing to an intrathoracic complication following surgery, the incidence of postoperative pulmonary lesions was quite high. With increasing use of routine chest roentgenography, the incidence of demonstrable complications has been shown to be considerably higher.

Rudnikoff and Headland had chest x-rays taken of forty consecutive patients who were being prepared for cholecystectomy. Chest x-rays were repeated on the fourth postoperative day and at the time of the patient's discharge. 'Positive postoperative chest x-rays were obtained in 28 to 70 per cent. In the majority, the chest x-ray findings were transitory but in seven

there were residual lung lesions at the discharge. Atelectasis and bronchopneumonia were most frequent. In many cases it was possible to make a differential diagnosis of the exact nature of pleuropulmonary lesions. In ninety patients undergoing abdominal operation, Palmer and Sellick found atelectasis in 65 per cent. In a duplicate series of ninety patients, whom certain preventive measures were instituted, the incidence declined to 9 per cent.

DISEASES INVOLVING ABDOMINAL VISCERA

Clinical Features

There are a number of intraabdominal diseases which may give evidence of their presence in the chest. The frequent occurrence of pulmonary infection and bronchiectasis in association with cystic fibrosis of the pancreas has been discussed in Chapter 2. In considering the pulmonary manifestations of abdominal disease, it is preferable to deal with the effects of these diseases, as a group, rather than with individual conditions. The occurrence of linear horizontal opacities in a chest x-ray, or the so-called 'comet tail' or 'pencil' shadows, or the finding of patchy basal infiltrations, or the detection of an appreciable amount of fluid in one or both pleural cavities are phenomena which may be associated with any of the abdominal diseases listed in Table 5. Weber and Gregg found that a gastric ulcer may be associated with chronic pulmonary disease, characterized by diffuse fibrosis and emphysema. This association does not hold for duodenal ulcer. These investigators reported a series of seventy cases of benign gastric ulcer in which chronic nonspecific pulmonary disease coexisted in 43 per cent. The suggestion was offered that some fundamental degenerative process related to aging, perhaps vascular, or other selective factor, may contribute to the development of the disease in both stomach and lungs.

Roentgenology

Any intrathoracic or intraabdominal disease which may interfere with diaphragmatic movement and cause shallow breathing may permit plugging of bronchi with secretion resulting in atelectasis. If the obstruction occurs in small bronchi

bronchioles, plate-like atelectasis may result. Under certain conditions, an effusion may also develop. In a study of 7,064 hospitalized cases, Marks and Nathan found twenty nine with linear atelectasis, 20 per cent occurring in patients with intrathoracic disease and 80 per cent with intra abdominal disease.

Fleischner was among the first to draw attention to the significance of these linear striations. This investigator suspected that the densities represented areas of atelectasis rather than pleural thickening, a belief held hitherto. The affected areas are projected as linear striations in the chest x ray because of the relative fixation of the mediastinum medially and the negative intrapleural pressure peripherally, thereby favoring vertical collapse of the involved portion of the lung. The disk like or plate like atelectatic areas appear in the chest x ray as linear streaks in one or both lower lung fields lying in more than one plane, at times in association with a pleural effusion.

The differential diagnosis of linear atelectasis and healed pulmonary infarcts which have shrunken asymmetrically may prove difficult. Linear atelectasis may also be duplicated roentgenologically by distended lymphatics incident to mitral stenosis and hypertension of the lesser circulation (see Chapter 11). Nor is the condition easily distinguishable from interlobar pleurisies. On the whole, the significance of linear striations is more readily appreciated in the light of the clinical history than on the basis of roentgen findings alone.

Case 28 Male—Age 51

The patient was admitted to a city hospital with a three month history of thirty pounds weight loss, anorexia, cough, expectoration, diarrhea and abdominal cramps. He confessed to have been a moderately heavy beer drinker for some years. A chest x ray revealed fluid in the left pleural cavity and a linear density running across the right lower lung field (Figure 53A). The heart was not enlarged. Two chest aspirations yielded serous fluid SG 1.018 to 1.020 with a predominance of lymphocytes. The sputum did not reveal acid fast bacilli except for one questionable positive culture.

The patient was transferred to Seton Hospital with a presumptive diagnosis of tuberculosis. A

chest x-ray at this time, approximately two months after the initial examination, revealed fluid in the right pleural cavity and horizontal striations across the left lower lung field (Figure 53B). The liver was enlarged and there was possibly also ascites. Liver function tests indicated liver disease (cephalin flocculation ++, persistent reversal of A/G ratio). A month later a chest x ray showed absorption of the fluid in the right chest leaving several linear densities, seen best in the right lateral projection. The patient improved on a high caloric, high protein and high vitaminic diet.

The abdominal conditions listed in Table 5, which may cause pulmonary atelectasis of the type described may also provoke pleural effusion.

TABLE 5

ABDOMINAL DISEASES WHICH MAY BE ASSOCIATED WITH INTRATHORACIC LESIONS

Inflammatory Lesions

- Liver Abscess
- Subdiaphragmatic Abscess
- Acute Cholecystitis
- Subacute Pancreatitis
- Acute Pancreatitis
- Periappendiceal Abscess
- Perforated Peptic Ulcer

Neoplasms

- Ovary
- Gallbladder
- Ileum
- Transverse Colon

Miscellaneous Lesions

- Hepatic Carcinosis
- Incarcerated Abdominal Hernia
- Benign Gastric Ulcer (Weber and Gregg)

From Marks and Nathan. *Radiology*, 52:363, 1949.

fusion. In most instances the pleural effusion is due to direct extension of disease to the diaphragmatic pleura. In the presence of an acute subdiaphragmatic disease, one may also encounter a transient, "sympathetic" effusion but usually the fluid is part of the infectious process.

Of particular interest is the finding of a large collection of fluid in the chest, usually a right-sided hydrothorax, accompanied by ascites in patients with cirrhosis of the liver and intraabdominal neoplasms notably ovarian tumors, to be described shortly. Williams reported fifteen cases of cirrhosis of the liver with pleural effusion. Six of these had antecedent ascites and eight had



Figure 53 Case 28 Cirrhosis of liver with pleuropulmonary metastases. A (Left) Obliteration of left costophrenic angle by fluid. B (Right) Large collection of fluid in right pleural cavity. C (Left) Horizontal line in left lower lung field. D (Right) Horizontal line in right lower lung field.

coincidental cardiac or pulmonary diseases. On the other hand, fifty-four patients showed ascites for considerable periods without demonstrable pleural effusion. Christian reported a case of bloody pleural fluid, an unusual complication of cirrhosis of the liver. A similar case was studied recently at the Montefiore Hospital.

Meigs Syndrome

The association of benign ovarian tumors as cysts and hydrothorax has been known for many years but the condition was not generally recognized as a clinical entity until Meigs and Cass in 1937 focused attention on this rather bizarre combination now known as *Meigs syndrome*. Heretofore the discovery of a pelvic or abdominal mass with pleurisy and ascites was immediately ascribed to advanced malignancy and the patient left to die of a presumably hopeless disease. The rapid reaccumulation of the fluid in the chest and abdomen after repeated aspiration seemed all the more in keeping with a malignancy.

The importance of recognizing Meigs syndrome lies in the fact that upon removal of the

pelvic tumor the fluid in the chest and abdomen quickly absorbs and the patient makes a complete recovery. In the original communication by Meigs and co-workers the underlying cause was found to be a fibroma of the ovary. The list of tumors has since been enlarged to include pseudomucinous cysts of the ovary, theca and granulosa cell tumors, fibroidenomas, uterine tumors, and even malignant pelvic tumors with ascites and hydrothorax but without demonstrable cancer cells in the ascitic or chest fluid. On several occasions in which I encountered instances of presumably the last mentioned sooner or later they turned out to be malignant tumors with serosal metastases.

It is noteworthy that myxedema may be associated with ascites and hydrothorax or hydropericardium without associated cardiac failure. Such an occurrence in a female would have to be differentiated from Meigs syndrome. Watson and co-workers noted in one patient with myxedema that the ascitic fluid gave a positive reaction for mucin. These investigators suggest that such effusions might represent an outpouring of mucinous fluid from serous surfaces analogous

to the accumulation of mucinous fluid in other tissues of patients with myxedema. Ferrazoni and Sprague also reported a case in which myxedema was associated with hydrothorax and ascites. There was no evidence of heart failure to account for the serous effusions. The effusions regressed after the administration of desiccated thyroid.

The manner of development of hydrothorax in Meigs' syndrome has provoked considerable speculation. Were the mechanism known, it would probably explain also the occurrence of hydrothorax in patients with cirrhosis of the liver, pseudocysts of the pancreas and the several other conditions associated with hydrothorax listed previously. Undoubtedly, many patients with ascites develop fluid in the chest that is not recognized clinically. There is also reason to suspect the hydrothorax rarely occurs without ascites although the presence of the latter cannot always be detected. Meigs quotes Cullen to the effect that "nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid." In Meigs' experience this held true for about 75 per cent of fibromas.

The relative infrequency of massive hydrothorax, in the presence of ascites of whatever cause, speaks for an interplay of several factors. The diaphragm is richly supplied with lymphatics and it takes only a few minutes for the transfer of particulate matter from the peritoneum to the subpleural lymph nodes and vessels. The major part of the material is carried by the subpleural lymphatics to the dorsal surface of the sternum and thence to the right lymphatic and thoracic ducts. I. C. Rubin and co-workers, in a series of animal experiments, using human serum as well as saline stained with carmine or India ink injected into the abdomen, found that the transfer of fluid from the abdominal into the pleural cavity is not obstructed from below upward but that resorption from the pleural cavity is apparently delayed. Small corpuscular elements like carmine and India ink are easily transported from the abdominal into the pleural cavities. The preponderance of right-sided hydrothoraces is assumed to be favored by the better development of the diaphragmatic lymph

channels on the right side, the greater activity of the right leaf of the diaphragm and the fact that the pulmonary lymphatic drainage takes place almost entirely through the right lymphatic ducts. A possible hormonal origin of Meigs' syndrome has also been suggested.

Cowan and co-workers had a unique opportunity to investigate the transport of particulate matter between the pleural and peritoneal cavities in a woman of sixty-one who had an ovarian carcinoma with ascites and hydrothorax. In an attempt to repress the ascitic fluid formation and the tumor growth, the patient was treated with radioactive colloidal gold (Au^{199}). As an incidental finding it was noted that a rapid transport of radioactive gold occurred from the peritoneal cavity to the pleural space. A maximum concentration was obtained within two hours. Radioactive gold was found in the abdominal cavity following right pleural space administration with a maximum concentration in one hour. The per cent of dose delivered to the opposite cavity in each instance spoke against a direct communication, rather, for some form of rapid transdiaphragmatic lymphatic transport.

There is, however, the possibility that in some cases an abnormal communication may be present between the pleural and peritoneal cavities. Williams reported a case in which a pleural effusion was apparently due to rupture of the diaphragm in a patient with longstanding ascites due to Laennec's cirrhosis of the liver. Emerson and Davies point out that the occurrence of a massive hydrothorax complicating ascites due to cirrhosis of the liver is characterized by a sudden onset, the appearance of the hydrothorax often coinciding with considerable diminution in the amount of ascites. In a well documented case, they cite an instance where it was possible to show, both by injection of dye into the peritoneal cavity as well as at autopsy, that a minute hole, less than 1 mm. in diameter, was present in the right hemidiaphragm due to a localized separation of the tendinous fibres, through which the ascitic fluid found its way into the pleural cavity. Were it not for the fact that the opening was stained with dye, it could have been easily overlooked. These investigators refer to two other

cases where a hydrothorax followed a diaphragmatic defect. It may be pertinent to mention that in a review of thirty-six reported cases of spontaneous pneumothorax, complicating induced pneumoperitoneum, Shapiro found the pneumothorax to have occurred on the right side, in thirty-one. The cause was usually the result of rupture of herniated peritoneum through a weakened diaphragm.

The possibility of a congenital opening being present in the diaphragm causing Meigs' syndrome also arises. If the opening is small the liver may block the passage of fluid. Deacon reported the finding of a wide channel in one case through which fluid passed readily from the peritoneal to the pleural cavity giving rise to Meigs' syndrome. As a final note to a complex subject, it should be noted that in some cases ascites and hydrothorax are found in association with relatively small ovarian tumors and it is suspected that the latter may possess a marked secretory power.

Case 29 Female—Age 34

The patient was admitted to the Lebanon Hospital because of continued swelling of the abdomen

which she had first noted about five months. The patient had also noted lately of breath cough, loss of appetite and weakness. Examination revealed a thin woman with a distended abdomen. The chest revealed stasis at the right base, the fluid reaching to of the fourth rib in the axillary line (Figure 54A). Microscopic examination did not reveal tumor.

The presumptive diagnosis was multiple fibroids associated either with a papillary carcinoma of the ovary or a fibroma of the ovary.

At operation, a massive pseudomucinous tumor of the right ovary and a intramural fibroid were found. The ovarian tumor occupied the right part of the abdominal cavity. About two liters of free fluid similar to that present in the cyst was free in the abdominal cavity. The left ovary appeared normal. Microscopic examination revealed cysts lined by a single layer of cells of the mucinous or goblet type. The structure of the cyst wall was composed of rather cellular tissue which was quite vascular. There was no histologic evidence of malignant tissue. Following removal of the cystic ovary, the pleural effusion and ascites quickly disappeared and the patient made an uneventful recovery (Figure 54B).

Pulmonary Manifestations of Metastatic Diseases

INTRODUCTION

There are many circulatory borne diseases which may affect the lungs. The incidence of pulmonary involvement and the patterns as summed by the metastatic lesions depend on the nature of the primary disease and the pathways taken by the pulmonary metastases. The physical examination of the chest gives no inkling of the presence or absence of metastatic deposits in the lungs. Let alone the appearance of the individual foci. Before discussing several representative forms of metastatic disease which may affect the lungs, it is in order to describe the avenues by which emboli originating in distant parts of the body may gain access to these organs.

PATHWAYS OF PULMONARY METASTASES

Anatomical Considerations

The pulmonary artery, carrying venous blood,

arises from the conus arteriosus in the upper part of the right ventricle. The artery comes upward and backward and then divides into right and left branches, the former passing behind the ascending aorta and superior vena cava, the latter, in front of the descending aorta. The branches of each pulmonary artery, after entering the hilus of each lung, follow closely the subdivisions of the bronchial tree, both structures being often encased in the same sheath. With each subdivision the artery rapidly diminishes in diameter so that by the time it reaches the terminal units of the lung the artery is one fourth or one fifth the size of the alveolar duct. Each blood vessel divides into as many ramifications as there are arterioles leading to alveolar sacs. The arterioles finally breaking up into innumerable capillary clusters which surround the alveoli. The blood becomes oxygenated as it passes through the capillary bed and is returned to

posterior surface of the left auricle by four veins which have no valves

In addition to the pulmonary or lesser circulation, the lungs possess a bronchial blood supply, at systemic pressure, which nourishes the stroma. The bronchial arteries arise from the thoracic aorta, often from the upper thoracic intercostals, internal mammary and subclavian arteries. Two or three arteries accompany each bronchus and its subdivisions forming a rich anastomosing plexus about the bronchi, bronchioles, lymphoid tissue and lymph nodes, the connective tissue septums and pleura. They form the vasa vasorum of the pulmonary artery. There is some overlapping in the capillary distribution of the pulmonary and bronchial arteries supplying the alveolar ducts. It should be noted that the bronchial arteries in man, supply the pleura and this may serve to explain the unusual vulnerability of the pleural serosa to metastatic deposits. Distinct bronchial veins are found only at the hilus of the lung, the smaller tributaries arising at the site of bronchial divisions. The greater part of the blood of both bronchial and

pulmonary arteries is returned by way of the pulmonary veins.

Pathological Considerations

The pulmonary arteries are, in health, end arteries and do not anastomose with the bronchial vessels, the capillary bed between the two systems maintaining functional rather than anatomic continuity. The transitional zone is a favorite site of bacterial lodgement. However, under abnormal conditions in response to increased demand for oxygen, the bronchial arteries become dilated, their ramifications more numerous and the capillaries between the pulmonary and bronchial arteries increase in size.

In a series of observations on the bronchial arterial circulation in the normal dog's lung, which is strikingly similar to that in man, Ellis and co-workers found that the bronchial arteries are necessary for the nutrition of the main stem and lobar bronchi in the region of the hilus. Distal to the hilar region the blood supplied by the pulmonary artery can maintain the integrity of the pulmonary tissue and the bronchial walls.

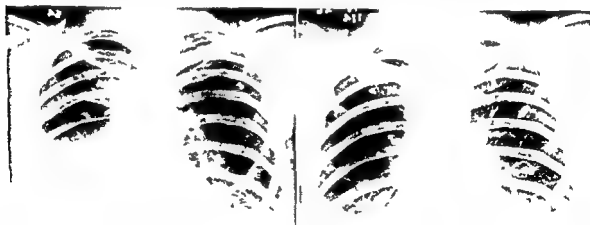


Figure 54. Case 29. Meigs syndrome. A (Left). Fluid in right pleural cavity, extending along mediastinum and dipping into small fissure. B (Right). Considerable decrease in size of the pleural effusion (after extirpation of a cystic ovary). (From Rosenfeld. *New York State J. Med.*, 48:527, 1948.)

It would seem therefore that under normal conditions the bronchial arterial circulation is probably not essential for nutrition of the peripheral parts of the lungs. In fact they found that the bronchial circulation may actually be a contributing factor to the development of pulmonary infarction after embolism. The hemorrhage that occurs in the pulmonary tissue after pulmonary embolism may come from the bronchial circulation.

Fillis and co workers comment that the bronchial arteries may be considered a vestigial circulatory system important to the fetus before birth but of little significance under normal conditions after birth except in the region of the hilus. When pathologic processes involve the lungs this vestigial blood supply may again be called upon to fulfill an important nutrient function. In support of this belief they cite the anatomical studies of Marchand and co workers who found that the size of the bronchial arteries in the human fetus is nearly the same as that of the adult whereas a great expansion occurs in the pulmonary artery vascular system after birth.

The removal of the physiologic screen between the lesser and greater circulations not only increases the blood flow to the tissues, thus possibly serving a useful purpose but may also act adversely by allowing the passage of bacteria and carcinomatous emboli between one system and the other also by permitting admixture of venous and arterial blood. Studies by Liebow and co workers also Prinzmetal and co workers and others have drawn attention to the many potential channels between the pulmonary artery and vein as well as between the bronchial and pulmonary arteries. Liebow and co workers showed that specimens of lung removed surgically from patients with bronchiectasis and prepared for study by the vinylite corrosion technique showed great enlargement of the bronchial arteries and numerous anastomoses of these vessels with the pulmonary arteries. The communications were multiple and usually occurred in the walls of the bronchiectatic sacs. In half of the specimens the anastomoses equalled or exceeded 1 mm in diameter. The anastomoses were so large and numerous as to suggest that they have

physiologic importance in shunting pulmonary arterial blood away from diseased tissue into relatively intact parenchyma and as a factor producing hypertension in the pulmonary circulation.

In a study of the bronchial pulmonary vascular shunts in patients with pulmonary tuberculosis, bronchiectasis and pulmonary cysts, Roosenburg and Deenstra demonstrated an increased blood supply from the bronchial arteries via anastomoses to the pulmonary arteries. The oxygenated blood from the systemic circulation flowing primarily via the normal route to the bronchial veins draining into the pulmonary veins and partially through the pulmonary capillaries. Since in the presence of chronic pulmonary diseases little or no gas exchange takes place in the capillaries, the large pulmonary veins entering the left heart contain a variable degree of unoxygenated blood, a left-right shunt. The left-right shunt may account for as much as one third of the cardiac output and causes an added strain on the heart.

Conditions may also arise where the pressure in the pulmonary artery system may be so high as to overcome the normally higher pressure in the bronchial arterial system. The venous blood flows through the diseased parts of the lung where it is unable to take up an adequate supply of oxygen. The blood is returned to the pulmonary veins in a high degree of oxygen unsaturation. The mixed blood may thus reach the heart as a result of a left-right shunt having been converted into a right-left shunt. Until recently the recognition of these arterio-venous channels had been of interest primarily to experimental pathologists and physiologists. Lately the significance of these shunts has become of increasing importance to physicians and surgeons concerned with precise diagnosis and treatment of diseases of the heart and lungs.

3. PULMONARY EMBOLIZATION

Clinical Features

The incidence of pulmonary involvement of metastatic deposits from distant sites is determined by the avenues of transfer of embolic matter. Tumor cells or septic material enter the caval system, pass through the right side of the heart, the pulmonary arteries and finally lodge

in the capillaries. In a series of experiments on the histogenesis of blood borne metastases Baserga and Saffioti found that tumor emboli spontaneously released by the primary growth are most likely to consist of single or few tumor cells. Such tumor emboli lodge in the pulmonary vessels either by adhering to the endothelium of arterioles or by plugging the lumen of capillaries. In the arterioles the spread of tumor cells beyond the endothelial wall appears to be preceded by a phase of intraluminal growth. The trapped embolus penetrates the vessel wall and eventually develops into a full blown nidus. It may be mentioned parenthetically that cancerous emboli may be dormant in tissues for many years without showing invasive features.

More difficult to explain is the absence of pulmonary metastases in the presence of a generalized blood borne disease. This is exemplified in the occurrence of limited tuberculous meningitis secondary to urogenital tuberculosis or limited vertebral involvement secondary to cancer of the prostate breast or thyroid. Batson is largely responsible for clarifying such apparently paradoxical situations by drawing attention to the fact that a collateral circulation exists between the veins of the chest abdominal wall and vertebral column. The vertebral veins lie outside the thoraco abdominal cavity and communicate with the intercostal veins also the veins of the abdomen and with the azygos system of veins. Through the latter there is free communication with the posterior bronchial veins and the veins draining the parietal pleura. The pressure in this valvless venous system is low so that with every compression of the trunk during strain or cough the pressure is raised sufficiently to shunt the blood flow from the azygos channels into the vertebral system. The presence of this paravertebral collateral circulation may serve to explain the high incidence of intracranial metastases of septic bacterial or malignant origin without pulmonary involvement.

The manner of spread of malignant cells through the pulmonary lymphatics has aroused considerable interest because of certain clinical and roentgenological features associated with this form of tumor invasion. Diffuse carcinomatous

involvement of the lymphatics of the lungs and pleura may originate from a small bronchiogenic carcinoma. More often the pleuropulmonary implication is secondary to carcinoma of the stomach breast ovary thyroid pancreas or prostate. It is still not entirely clear as to whether the lungs are involved by retrograde extension from the hilar lymph nodes along peribronchial and subpleural lymphatics or whether the tumor cells invade initially the lungs by way of the pulmonary arteries gain access to the lymphatics and then spread to the hilar lymph nodes. Current opinion veers to the belief that the pleura and lungs are first involved by a hematogenous dissemination of tumor emboli by way of the thoracic duct subclavian veins and the pulmonary arteries. After the development of the tumor emboli in the pulmonary capillaries there is lymphatic permeation toward the hilar lymph nodes.

Irrespective of whether the neoplasm originates in a bronchus stomach pancreas or other organ the primary growth is apt to be insignificant even microscopic in size. Cut section of the involved lung reveals a firm organ with diffuse web like infiltrations along the lymphatics which appear as yellowish white streaks in places showing larger aggregations. The involvement is most pronounced in the mid and lower portions of the lungs. The lymphatics in the visceral pleura are dilated and streaked with glistening tumor tissue bringing into relief the individual lobules. The hilar lymph nodes are as a rule only moderately enlarged. This is possibly an additional indication that the original dispersion is peripheral rather than central.

It would take us too far afield to dilate on hematogenous tuberculosis pyemia disseminated coccidioidomycosis hematogenous amebic abscesses and other blood borne infections which may involve the lungs and pleura. The current use of specific antibacterial measures has reduced greatly the incidence of these once dreaded diseases so that they play a relatively minor role in medical practice. In contrast to metastatic pulmonary abscesses one is more apt to encounter bland emboli from phlebotrombosis of the veins of the lower extremities or pelvis. These



Figure 55 Forms of metastatic carcinoma of lung. A (Left) Numerous ovoid densities of uneven size are seen in both lungs especially in the lower lobes (Resection of a carcinoma of the colon five years previously) B (Right) Reticular striations permeating both lung fields especially the lower portions circumscribed focus in right upper lobe (Lymphangitic carcinomatosis of the lungs secondary to carcinoma of the thyroid circumscribed focus in right upper lobe was found at autopsy to be a hamartoma)

emboli are more apt to cause pulmonary infarction, the features of which will be described in the following chapter

Theories of Selective Localization of Pulmonary Emboli

There is one aspect to the problem of metastatic pulmonary disease which may be appropriately discussed at this time, namely, why some forms of hematogenous implantations favor the upper lobes and others the lower lobes. The theories proposed, and they have been many, concern themselves chiefly with explanations for the predilection of reinfection tuberculosis for the apices of the lungs. However they have a certain bearing also on the entire problem of pulmonary metastases.

Doel postulates that a relative ischemia, due to the relatively lower pulmonary pressure is the cause of apical localization of tuberculosis and for the same reason for the low incidence of progression of the disease in this location. Medlar

and Sasano evolved an 'upright theory' by which it is postulated that the entire lung is at first uniformly seeded but that the tubercle bacilli disappear from the lower lobes and progress in the upper lobes as a result of the inadequate blood circulation of the apices in the upright man. In a series of experiments in rabbits these investigators found that when the animals were forced to sit upright, the lesions were more numerous in the upper lobes.

Smith and co-workers found that the upper lobes are infected with tuberculosis directly and immediately because the 'stream flow' of blood through the heart is directed to the upper lobes. They conclude that the apical lesions in tuberculosis do not depend upon inadequate circulation rather on the position of the animal which determines the path taken by the stream flow of blood through the heart. In other words they confirm the observations of Medlar and Sasano but not the interpretation. Using animals as well as synthetic plastics Smith and co-

PULMONARY MANIFESTATIONS OF ABDOMINAL AND METASTATIC DISEASES

183

workers studied the problem not only with respect to tuberculosis but also with respect to pulmonary emboli and infarcts which favor the lower lobes. According to their stream flow theory it is postulated that in the case of tuberculosis pus or small caseous particles discharged from infected lymph nodes and carried by way of the thoracic duct and left subclavian vein to the right auricle, right ventricle and into the pulmonary artery are deposited in the upper lobes because there is little mixing of the blood in the upper stream with that entering the same chambers by way of the inferior vena cava. Each column of blood is presumed to pass in a liver through the right side of the heart into the upper and lower parts of the lung respectively. The stream flow theory according to these

investigators explains the apical localization of tuberculosis, also the basal preference of emboli and infarcts arising in foci of phlebothrombosis in veins of the lower extremities and abdomen. According to this theory blood borne metastases to the lungs follow the simple hydrodynamic principle that fluid of the same viscosity may flow side by side through tubes for considerable distance with a minimum of admixture. The stream flow theory is the seventeenth one proposed to explain why different metastatic diseases of the lungs favor particular parts of the organs. There will probably be additional theories.

ROENTGENOLOGY OF METASTATIC PULMONARY LESIONS

As indicated the site of the primary tumor



Figure 56. Alveolar cell carcinoma of lung (Pulmonary adenomatosis) simulating metastatic neoplasm. A (Left) Ill defined single and confluent densities scattered in both lungs (Clinical course characterized by loss of weight increasing dyspnea and profuse mucoid expectoration. Smears from bronchoscopic washings and from sputum showed cells suggestive of alveolar origin. Total duration of the disease from onset of striking symptoms to death fifteen months.) B (Right) Microscopic section of lung shows mucus secreting tumor lining alveolar septa. Alveoli filled with mucus with nests and cords of exfoliated tumor cells. (Gross appearance of lung resembled a pneumonia in a gray stage of hepatization.)



Figure 57 Solitary metastasis of lung A (Left) Large, ovoid density in left midlung B (Right) After resection of left lower lobe (Specimen revealed malignant melanoma primary growth appeared in right shoulder six years previously, treated with radiotherapy and later with radical excision metastases appeared in pelvis several months after operation)

and possibly the avenues by which the lungs are invaded, determine the nature of the metastatic lesions. Tumors of the breast and stomach are apt to spread to the lungs and pleura by way of the lymphatics either through the thoracic or right lymphatic ducts. Tumors in organs closely associated with the systemic venous circulation, such as renal and skeletal malignancies, show a particularly high incidence of pulmonary metastases. Although pelvic tumors may spare the lungs careful postmortem studies show frequent pulmonary involvement. In a correlative study of the postmortem and roentgen findings of a large number of patients treated at the Montefiore Hospital, Fried found pleural or pulmonary involvement in 54 per cent of renal neoplasms, in 43 per cent of cancer of the prostate but in only 7 per cent of cancer of the bladder. Willis found pulmonary metastases in 30 per cent of all fatal cases, being present in 75 per cent each of instances of chorionepithelioma, osteosarcoma and renal carcinoma, 65 per cent of carcinoma of the thyroid, 60 per cent of melanoma,

55 per cent of carcinoma of the breast, 40 per cent of carcinoma of the esophago-gastrointestinal tract, 30 per cent of oral and pharyngeal carcinoma, 20 per cent each of hepatic and pancreatic malignancies, 15 per cent of uterine malignancy and 10 per cent of ovarian carcinoma.

With occasional exceptions, metastatic tumors spreading through blood channels involve both lungs with nodular densities varying in size from millary to large masses. Occasionally the chest x-ray reveals a solitary, circumscribed lesion and unless one is aware of the nature of the primary disease, the differential diagnosis between a primary and metastatic lesion may be quite difficult. Lymphangitic carcinomatosis permeating the lungs and pleura is characterized by a diffuse reticulation interspersed with nodulations affecting symmetrically both organs. If the primary focus is in the lung, the lymphatic spread may be regional.

Although a number of attempts have been made to classify the roentgenologic appearances of metastatic pulmonary neoplasms into various

patterns such as miliary, nodular (Figure 55A), infiltrative, lymphangitic (Figure 55B), massive and cavitating forms, clear-cut differentiations are not feasible and of minor clinical significance. Primary carcinoma of the lungs may simulate metastatic disease (Figures 56A and B). Of more practical importance is the fact that a solitary metastasis in a lung may be amenable to resection and the life of the patient prolonged. Unfortunately, resectable pulmonary tumors are met in a very small percentage of patients with metastatic cancer (Figures 57A and B). In an analysis of 314 cases of metastatic pulmonary neoplasms observed in a five-year period, Minor found two cases in which resection was actually carried out. These two patients were still alive and free of malignant disease more than four and seven years after their pulmonary resections. It is noteworthy that the first record of a successful resection for metastatic cancer of the lung was reported by Barney and Churchill in 1939. The particular patient had had a nephrectomy for a hypernephroma fifteen months previously and

was alive and well twelve years after the lobectomy.

In 1950, Seiler and co workers found reports of sixty-eight cases treated by resection for metastatic pulmonary lesions. The tumors most frequently resectable are those secondary to carcinoma of the large bowel (eleven cases), hypernephroma (seven cases), fibrosarcoma (seven cases) and carcinoma of the ovary (five cases). With several exceptions, the patients with long intervals of time elapsing between the occurrence of the primary and the secondary tumors did no better than the group as a whole. Bronchial involvement was noted in 63 per cent of the cases in which the reports especially mentioned this feature or in 27 per cent of the entire group. Higginson found bronchial involvement in nine of thirty-five cases. In eight of these (22.8 per cent) bronchoscopic biopsy was positive. Of the thirty-five pulmonary metastatic malignancies, twenty-six came to surgical exploration and of these, twenty-two were resected. In two patients, two or more resections were done for re-



Figure 58. Case 30. Solitary metastasis to lung three years after resection of a portion of colon for adenocarcinoma. A (Left). Circumscribed density in right middle lobe. B (Right). After excision of right middle lobe (Microscopic examination of tumor revealed adenocarcinoma identical in appearance with that resected from the colon.)



Figure 59 Metastatic carcinoma of bronchus primary in the colon. A (Left) Triangular density at base of right upper lobe adjacent to the hilum, above horizontal fissure which is accentuated and slightly displaced upward (Expectorated piece of tissue revealed histologically adenocarcinoma. Bronchoscopy showed an obstruction of the right upper lobe bronchus. Biopsy specimen also revealed adenocarcinoma.) B (Right) Two months later considerable diminution in size of the density. (Patient died six months later of generalized carcinoma.) (See Figure 87.)

current metastases. Metastatic pulmonary malignancies secondary to carcinoma of the large bowel offered the best prospects of resectability.

Case 30 Female—Age 59

Three years previously the patient had a resection of a portion of the colon for adenocarcinoma. She felt well until late in 1954 when she developed pain in the right lower chest, moderate cough, expectoration, slight dyspnea on exertion and wheezing. The physical examination was noninformative. The chest x-ray showed a well circumscribed density in the region of the right middle lobe (Figure 58A). In view of the past history of carcinoma of the bowel it was suspected that the lesion in the lung represented a metastatic deposit although a primary carcinoma of the lung could not be excluded. The patient was admitted to the Montefiore Hospital. A bronchoscopy was negative. A search for possible metastases elsewhere in the body was unrevealing.

On December 17, 1954 the patient was operated on by Dr. Morris Rubin. The pleural cavity contained no free fluid and there were no visible metastases. Palpation of the mediastinum and hilum revealed no abnormalities. The upper and lower lobes

appeared normal. The right middle lobe was completely shrunken and contained a mass about the size of a large walnut. Further inspection revealed no other masses or enlarged lymph nodes. In view of these findings, the right middle lobe was resected. The specimen revealed a well circumscribed mass of grossly recognizable tumor. It was pale, yellowish gray with foci of necrosis. The bronchi leading to the tumor were not invaded. The surrounding tissue appeared grossly unremarkable. The microscopic examination showed the tumor to be composed of well developed adenocarcinoma. The bronchi showed no evidence of malignant changes. The tumor itself appeared compatible with metastatic carcinoma originating in the bowel. A review of the microscopic sections of the previously resected colon showed identical histological features.

After operation the upper and lower lobes expanded completely and the patient was discharged two weeks later in good condition (Figure 58B). She has remained well without signs of recurrence of the disease, when examined one year later.

Rare instances are on record of malignant tumors metastasizing to the trachea or bronchi which may simulate primary tumors. Cohen re-

ported an instance of a solitary pulmonary metastasis with detectable bronchial involvement which appeared nine and a half years after resection of a colon carcinoma. The author found reports of thirteen additional cases in which bronchial invasion by a pulmonary metastasis was demonstrated endoscopically. I have had a similar experience. The patient, a physician aged sixty-one, had had a resection of the sigmoid colon four years previously. The present illness began with cough and expectoration. On one occasion the patient spat up a small piece of tissue which on histologic examination revealed adenocarcinoma similar to that obtained from the resected colon. At this time also the chest x-ray showed a density at the base of the right upper lobe near the hilum immediately above the horizontal fissure which was accentuated and displaced upward (Figures 59A and B). Auscultatory findings were in keeping with bronchial

obstruction, the latter being confirmed on bronchoscopy, the biopsy specimen also revealed metastatic carcinoma. The patient died six months later.

It is well to bear in mind that although lesions found in the lungs of patients who have had previous resections may be assumed to be metastatic, occasionally one may be dealing with a second primary in the lung. With the marked increase in bronchiogenic carcinoma this possibility is more than of academic importance. Poppe encountered four patients with primary carcinoma of the lung who had had previous resections of the large bowel for primary malignancies. Three of these had been allowed to reach an inoperable stage, on the assumption that the lung tumor was metastatic from the rectum. Poppe concludes that a more optimistic attitude about resecting metastatic pulmonary malignancies may save a few patients with primary carcinoma of the lung.

Bibliography

PULMONARY MANIFESTATIONS OF ABDOMINAL DISEASES

- BRICK, I. B. Incidence of Hiatus Hernia and Associated Lesions Diagnosed by Roentgen Ray. *Arch Surg* 58: 419, 1949.
- CHRISTIAN, A. H. Bloody Pleural Fluid An Unusual Complication of Carcinoma of the Liver. *Ann Int Med* 10: 1621, 1937.
- COVANN, I. I., CROW, H. S., BURGESS, G. F., and KARRIOTT, F. G. Transport of Radioactive Colloidal Gold Between Serous Cavities. *Surg Gynec & Obst* 98: 721, 1954.
- DEACON, A. L. A Case of Meigs Syndrome with an Ovarian Carcinoma. *Brit M J*, 1: 317, 1954.
- FERRAYOURN, R. R., and SPRAGUE, R. G. Myxedema with Ascites and Hydrothorax. *Proc Staff Meet Mayo Clin* 27: 15, 1952.
- FLAISCHNER, F. Plattenformige Atelektasen in den Unterlappen der Lunge. *Fortschr Geb Röntgenstrahlen* 54: 315, 1956.
- FREDMAN, R. L. Intrapulmonary Pleural Effusions. *Am J Roentgenol* 71: 613, 1954.
- GROSS, R. J., NELL, R., and LORR, W. Pseudocyst of the Pancreas Associated with Hydrothorax. *Am J Roentgenol* 67: 585, 1952.
- JENKINSON, E. L., and ROBERTS, E. W. Lesions of the Diaphragm. *Am J Roentgenol* 38: 584, 1937.
- JONES, H. B. Basal Pleural Fluid Accumulations Resembling Elevated Diaphragm. *Radiology* 50: 727, 1948.
- KIRALIN, H. R., and GILBERTSON, E. L. Roentgenograms of Thorax That Suggest Carcinoma of Stomach. *JAMA*, 134: 1228, 1947.
- LAPOINTE, H. Diaphragmatic Hernia. *J Canad A Radiol* 2: 65, 1951.
- MARAS, J. L., and NATHAN, A. The Linear Atelectatic Sign in Intra Abdominal Lesions. *Radiology* 52: 361, 1949.
- NICHAY, D. G., SPARKLING, H. J., JR., and ROBBINS, S. L. Carcinoma of the Liver with Massive Hydrothorax. *Arch Int Med* 79: 501, 1947.
- MEIGS, J. V., and CASS, J. W. Fibroma of the Ovary with Ascites and Hydrothorax. *Am J Obst & Gynec* 33: 249, 1937.
- O'CONNOR, T. J., and RITVO, M. Diagnosis of Hiatus Hernia on Plain Roentgenograms of Thorax and Abdomen. *JAMA* 157: 113, 1955.
- PALMER, H. S., and SELICK, H. A. The Prevention of Postoperative Pulmonary Atelectasis. *Lancet* 1: 164, 1953.
- RICHMAN, S., and BARRY, W. F. Jr. Localized Bulge of the Right Diaphragm Simulating Neoplasm. *Am J Roentgenol*, 77: 27, 1954.
- ROSENFELD, S. S. A Pseudomucinous Cyst of the Ovary with Ascites and Hydrothorax. *New York State J Med* 48: 527, 1948.
- REBIN, I. C., NOVAK, J., and SOLINE, J. J. Ovarian Fibromas and Theca Cell Tumors. Report of 78 Cases with Special Reference to Production of Ascites and Hydrothorax (Meigs Syndrome). *Am J Obst & Gynec*, 43: 601, 1944.
- RUDEKOFF, I., and HEADLAND, G. I. Pulmonary Changes Following Cholecystectomy. *JAMA* 146: 989, 1951.
- SANTE, L. R. Basal Exudates of Subphrenic Origin. *Am J Roentgenol* 44: 350, 1940.
- SHAPIRO, M. Spontaneous Pneumothorax Complicating Pseudoperitoneum Therapy. A Review and Report of a Case. *Am Int Med*, 43: 876, 1955.
- TEPLICK, I. G., and MAYER, S. H. Right Sided Thoracic Stomach. *Am J Roentgenol* 58: 196, 1947.

- WALLINGFORD, A. J. Ascites in Gynecology with Special Reference to a Possible Hormonal Origin of Meigs Syndrome. *New York State J Med* 55:221 1955
- WATSON, C. J. CRAIG D. and BEACH N. Myxedematous Ascites. *Internat Clin* 4:176 1941
- WEBER J. M. and GREGG L. A. The Coincidence of Benign Gastric Ulcer and Chronic Pulmonary Disease. *Ann Int Med* 42:1076 1955
- WEENS H. S. Pulmonary Disease Associated with Mega Esophagus. *Am J Roentgenol* 52:477 1944
- WILLIAMS M. H. JR. Pleural Effusion Produced by Abdominal Pleural Communication in a Patient with Laennec's Cirrhosis of the Liver and Ascites. *Ann Int Med* 53:16 1950
- WOOLRIDGE, W. E. and HAGENMAN P. O. Benign Pelvic Tumors with Ascites and Hydrothorax. *Am J Med* 5:737 1948
- ### PULMONARY MANIFESTATIONS OF METASTATIC DISEASES
- ABERNATHY R. S. SMITH G. B. JR., and SMITH D. T. Selective Localization of Experimental Emboli. *Am Rev Tuberc* 70:557 1954
- BARNEY J. D., and CHURCHILL, E. D. Adenocarcinoma of the Kidney with Metastasis to the Lung Cured by Nephrectomy and Lobectomy. *J Urol* 47:769 1939
- BARBERA R. and SAFFIOTTI U. Experimental Studies on Histogenesis of Blood Borne Metastases. *Arch Path* 19:26 1915
- BATSON O. V. The Function of the Vertebral Veins and Their Role in the Spread of Metastasis. *Ann Surg* 117:138 1940
- BONDURANT S. and SMITH D. T. The Mechanical Basis for the Layering of Blood in the Right Heart and Pulmonary Artery as Revealed by the Injection of Synthetic Plasters. *Am Rev Tuberc* 70:570 1954
- COLLEN A. G. Solitary Pulmonary Metastasis with Detectable Bronchial Involvement Appearing Nine and a Half Years After Resection of Colon Carcinoma. *New York State J Med*, 50:1848 1950
- COVIAN D. R. and DeLONG R. P. The Role of the Vertebral Venous System in the Metastasis of Cancer to the Small Colon. *Cancer*, 4:610 1951
- DOCK W. Reasons for the Common Anatomic Location of Pulmonary Tuberculosis. *Radiology* 48:319 1947
- DONCE, M. SCHMIDT H. W., and McDONALD J. R. Metastatic Malignant Lesions of the Bronchus. *Proc Staff Meet Mayo Clin* 23:391 1948
- ELIOT F. H. Bronchial Cancer of the
- GHOREE, A. A., and KARSNER H. T. A Study of the Relation of Pulmonary and Bronchial Circulation. *J Exper Med* 18:500, 1913
- HAROLD J. T. Lymphangitis Carcinomatosa of the Lungs. *Quart J Med*, 21:353, 1952
- HICHTONSON J. F. A Study of Excised Pulmonary Metastatic Malignancies. *Am J Surg* 90:241 1955
- LACHMAN I. Paradoxical Metastasis and Transpulmonary Cancer Spread. *Am J Roentgenol* 72:499 1954
- LEWIS A. A. HALES M. R., HARRISON W., BLOOMER W., and LINDSLOC, G. F. The Genesis and Functional Implications of Collateral Circulation of the Lungs. *Isle J Biol & Med* 27:637 1950
- LEWIS A. A. HALES M. R. and LINDSLOC G. F. Enlargement of the Bronchial Arteries and their Anastomoses with the Pulmonary Arteries in Bronchiectasis. *Am J Path* 25:211 1949
- MARCHAND P. GILROY J. C. and WILSON V. H. An Anatomical Study of the Bronchial Vascular System and Its Variations in Disease. *Toray*, 5:207, 1950
- MARSH J. L. Metastatic Tumors of the Lung. *Dis Chest* 17:63 1950
- MEDLAR, E. M., and SASAKO K. T. A Study of the Pathology of Experimental Pulmonary Tuberculosis in the Rabbit. *Am Rev Tuberc* 34:456 1936
- MILLER, W. S. *The Lung* Springfield Illinois Charles C. Thomas Publisher 1937
- MINOR G. R. A Clinical and Radiologic Study of Metastatic Pulmonary Neoplasms. *J Thoracic Surg*, 20:34 1950
- MORGAN A. D. The Pathology of Subacute Cor Pulmonale in Diffuse Carcinomatosis of the Lungs. *J Path & Bact* 61:75 1949
- POPPE J. K. Discussion of article by Higginson. *Am J Surg* 70:741 1955
- PRINZMETAL, M. ORVITZ E. M., JR. SMILIN B. and BERMAN H. C. Arteriovenous Anastomoses in Liver Spleen and Lungs. *Am J Physiol*, 152:48 1948
- ROOSENBURG, J. G., and DEENSTRA H. Bronchial Pulmonary Vascular Shunts in Chronic Pulmonary Affections. *Dis Chest* 28:664 1954
- SAILER H. H. CLAGETT O. T., and McDONALD J. R. Pulmonary Resection for Metastatic Malignant Lesions. *J Thoracic Surg* 19:655 1950
- SMITH D. T. ABERNATHY, R. S. and SMITH G. B. JR. The Stream Flow Theory. *Am Rev Tuberc* 70:547 1954
- TURNER J. W., and JAFFE H. L. Metastatic Neoplasms. A Clinical and Roentgenological Study of Involvement of Skeleton and Lungs. *Am J Roentgenol*, 43:479 1940
- WILLIS R. A. *The Spread of Tumors in the Human Body* London Butterworth 1952
- WOOD D. A., and MILLER M. The Role of the Dual Pulmonary Circulation in Various Pathologic Conditions of the Lungs. *J Thoracic Surg*, 7:649 1938

✓ Pulmonary Manifestations of Cardiovascular Diseases

Introduction

THE BLOOD FLOW through the heart and lungs is so finely adjusted that any interference with the circuit is quickly felt in both organs. For the moment we are concerned with disturbances in the cardiovascular apparatus which may be reflected in the lungs to a significant degree. Certain features relating to the blood supply of the lungs were discussed in the preceding chapter in relation to metastatic pulmonary disease. The following will deal more specifically with cardiovascular pulmonary derangements. One cannot

separate cardiopulmonary functional disturbances and intrinsic disease of blood vessels or the latter and resulting parenchymal lesions. The order in which the several morbid states will be considered is therefore not intended to serve as a nosological classification of cardiopulmonary disease. The description will be limited to basic mechanisms and the more prominent clinical features of the several conditions mentioned, with special reference to the chest x-ray findings.

Cardiopulmonary Dynamics

The right side of the heart, the depot of the pulmonary circulation, accommodates the same amount of blood in a given unit of time as that discharged by the left side of the heart into the aorta and systemic circulation. The blood capacity of both lungs potentially equals that of the remainder of the body. Congestive heart failure is a sign that the right side of the heart is unable to accept and expel the venous blood brought to the right auricle and right ventricle. In time this gives rise to peripheral blood stasis and edema. The cause of the right ventricular failure may be a preexisting insufficiency of the left ventricle or disease of the pulmonary valves or disease of the lungs or blood vessels causing pulmonary hypertension and right heart strain.

The lungs ordinarily hold about 9 per cent of the total blood volume during inspiration and about 6 per cent during expiration. The systolic pulmonary pressure is only one-sixth that of the systemic (i.e., 20 mm of mercury). It is obvious, therefore, that under stress the lungs are able to accommodate many more times their normal load

Thus, when congestion occurs, a large volume of blood is able to accumulate in the lungs. In health there is a wide safety zone before the critical period is reached. Massive intravenous infusions may be introduced in the experimental animal without causing pulmonary edema unless the pulmonary venous pressure is increased by artificial means. The great adaptability of the lungs to increased demand is also evident from the following. After exercise the cardiac output may rise four-fold, from 5 liters per minute to about 20 liters per minute, whereas the pulmonary ventilation may increase more than fifteen-fold, from a resting minute volume of 8 liters to as much as 125 liters (Drenker).

The pressure and volume differences between the lesser and greater circulations are reflected in the relative muscular thickness of the two ventricles, the wall of the left ventricle being normally about twice as thick as that of the right. Other points of difference also exist between the pulmonary and systemic circulations, there being no interdependency between the one and

the other. The arterial pressure may be normal or even below normal in one and high in the other. The autonomy of functions between the greater and the lesser circulations may be determined by instrumental means as well as by the behavior of the circulation in the two systems in response to drugs. Intravenous administration of aminophylline causes an abrupt decrease in the arterial pressure of the greater circulation but does not have a hypotensive effect on the smaller circulation. Other drugs affect the two circulations in opposite manner. The lesser circulation has its own neuroregulatory system which is independent of that of the greater circulation.

In essence the right side of the heart stands in the same relation to the lesser circulation as the left side does to the greater circulation: the minute output of blood from the right ventricle equalling that ejected by the left ventricle. Inspiration not only fills the alveoli with air but also

aids in filling the capillaries with blood. Expiration helps to expel blood as well as air from the lungs. Disturbances in the mechanics of the lesser circulation react on respiration just as disturbances of respiration react on the lesser circulation. Likewise the symptoms of pulmonary and cardiac insufficiency, both primarily expressed in anoxia resemble each other so closely that one is often hard pressed to distinguish the one from the other. In advanced cardiopulmonary failure it may be a matter of academic interest whether the insufficiency is mainly cardiac or pulmonary; usually it is a combination of both. But before this stage is reached it is important to differentiate the two components in order to treat the impending breakdown intelligently. Recent studies with cardiac catheterization and cardiopulmonary function tests have served to shed considerable light on the subject especially on the role played by pulmonary hypertension.

Pulmonary Hypertension

PHYSIOLOGICAL CONSIDERATIONS

Many factors are at play in regulating the blood flow in the lesser circulation. The short wide pulmonary artery with its rapid subdivisions and immense capillary network placed between countless alveoli offers an ideal arrangement for complete oxygenation and speedy return of the blood by way of the four veins to the left auricle. It is noteworthy that the pulmonary arterioles have six to eight times the diameter of the arterioles of the greater circulation. The lung capillaries are also very wide. In heart failure associated with hypertension of the lesser circulation the lung capillaries may dilate ten to thirty times their normal size (Weiss).

Hypertension of the lesser circulation may arise under varied circumstances. In recent years a primary form of hypertension has been recognized associated with right ventricular hypertrophy and usually with variable degrees of pulmonary vascular sclerosis. No demonstrable cause is found in this type of so-called essential or primary hypertension there being no recognizable antecedent cardiac or pulmonary disease. Eventually symptoms and signs of right heart

failure appear. The important role played by vascular shunts in causing obstruction and hypertension of the lesser circulation was mentioned previously. Branton believes that primary pulmonary hypertension results from excessive entry of blood into the lesser circulation from the bronchial arteries. The blood injected under systemic pressure causes dilatation and sclerotic changes in the pulmonary artery and hypertrophy and eventual failure of the right ventricle.

In the vast majority of instances of pulmonary hypertension the increased pressure in the lesser circulation is secondary to some other disturbance including (1) obstruction of the lesser circulation beyond the pulmonary system as exemplified in mitral stenosis and a failing left ventricle of whatever cause and (2) obstruction within the pulmonary system either in the main pulmonary artery by an embolus or as a result of thrombosis of branches of the pulmonary artery by vascular fibrosis. The last mentioned is encountered in association with lymphangitic carcinomatosis, schistosomiasis, primary pulmonary arteriole sclerosis, polyarteritis nodosa and other diseases associated with widespread interstitial fibrosis and

capillary vascular involvement. In addition secondary pulmonary hypertension may be due to alterations in the thoracic cage as a result of thoracoplasty or kyphoscoliosis.

ROENTGENOLOGY

Signs of pulmonary hypertension are recognized in the chest x ray as a result of the secondary effects of the increased pressure in the heart and in the pulmonary blood vessels. In severe mitral stenosis associated with pulmonary hypertension the left hilum is frequently concealed by a dilated main pulmonary artery and its left branch. The right hilum is usually accentuated. The lung parenchyma shows loss of normal translucency due to a profusion of blood vessels. But it is difficult to reconcile the roentgen appearances of the latter in all cases with the angiographic observations of Goodwin and co-workers who found that in patients with pulmonary hypertension the main arteries are enlarged

but the distal branches are narrowed, irregular and tortuous especially in the lower lobes. These investigators found that the severity and extent of the vascular changes bore a close relation to the degree of pulmonary hypertension.

Attention has been recently drawn to the presence of small horizontal lines at the bases of the lungs as an indication of pulmonary hypertension in the presence of mitral stenosis (Figures 60A and B). These lines are sharp, well defined and are arranged in parallel fashion, one above the other near the costophrenic angles. The lines lie immediately beneath the pleura. Kerley found these lines in silicosis, pneumoconiosis and other diseases. Davies and co-workers noted these lines referred to as Lines B of Kerley in pulmonary hypertension. According to Kerley also Carmichael and co-workers these lines are presumed to represent overloaded intercommunicating lymphatics due to disturbed flow of the lymphatic circulation. It might be mentioned at



Figure 60. Advanced rheumatic heart disease with mitral stenosis and pulmonary hypertension showing Lines B of Kerley. A (Left): Markedly enlarged heart with prominent pulmonary conus. B (Middle): Increased vascular markings in lower lung zones arranged in parallel fashion near the costophrenic angles. C (Right): Detail of right lower lobe (Transbronchoscopic arterial pressure determinations revealed a mean pressure of 25 mm Hg).

this point that according to Dock the flow of lymph increases with the rise of venous pressure and is most rapid and effective at the lung bases

Short found that these striations or as he prefers to term them "septal lines" correspond both in size and distribution with the interlobular septa although Kerley believes the lines are too long to be interlobular septa. Short suspects that the lines represent ingrowths from the subserous areolar tissue that invests the lung. The interlobular septa are traversed by tributaries of the pulmonary venous system and also by the lymphatic channels that link the deep lymphatic system with the subpleural network. The prominence of the interlobular septa, according to Short must therefore be due to enlargement of one or more of these structures. At first the enlargement of the septa is due to edematous swelling of areolar tissue later from fibrosis. This may explain why in some cases septal shadows persist unchanged after relief of the stenosis. In the usual chest x-ray taken for cardiac disease the overexposed film is apt to miss the delicate striations.

Short studied the radiographic appearances of the lungs in thirty-three patients with rheumatic mitral stenosis in whom at operation or necropsy the maximum diameter of the mitral valve was 1 cm. or less. The lung architecture was abnormal in varying degrees in each patient. Septal lines were found in twenty-five cases and although never the sole abnormality they were sometimes the most impressive. Serial chest x-rays showed the changes to be persistent and slowly progressive. In Short's opinion a normal lung architecture is inconsistent with a diagnosis of severe mitral stenosis.

Pulmonary Arteriosclerosis

Sclerosis of the pulmonary artery and its larger subdivisions is quite frequent the condition increasing in incidence and degree with age. The process may be part of a generalized atherosclerosis affecting the entire vascular system or it may be present to a greater degree or even be limited to the pulmonary blood vessels. The pathologic changes consist initially in an increase of elastic tissue in the media of the smaller branches of the pulmonary artery. Soon there is intimal thick-

Confirmatory observations of the significance of these lines as an indication of pulmonary hypertension in patients with mitral stenosis have been reported by Levin. This investigator reviewed the chest x-rays of sixty-three patients with a clinical diagnosis of mitral stenosis. Each was studied by right heart catheterization, pulmonary artery pressure and twenty-seven of these also by pulmonary wedge pressure. Thirty-nine (39) patients showed typical septal lines. A positive correlation was found between the degree of basal striae and pulmonary artery and wedge pressures the higher the pressure the more frequent the basal striae. Current opinion favors the view that septal lines encountered in patients with hypertension of the lesser circulation are due to edema and associated distention of the lymphatics in the interlobular septa. Grainger and Hearn found the lines in predominant mitral regurgitation as well as in mitral stenosis. They did note however that patients with predominant mitral stenosis showing septal lines on their preoperative chest x-ray almost invariably improved after a technically successful valve operation.

I have noted basal striations of the type described in patients in whom there was no reason to suspect pulmonary hypertension (see Figures 14 and 15). Grainger and Hearn state that septal lines are seen in any condition in which there is impairment of pulmonary lymphatic drainage. These include lymphangitic carcinomatosis, Hodgkin's disease, leukemia, pneumoconiosis after ligation of the thoracic duct and with any form of reticulosis affecting the mediastinal lymph nodes.

ening and later fibrous tissue reaction and obliteration of the vessel lumen by organized thrombi and intimal proliferation. Recanalization is often seen.

The diseases leading to hypertension in the lesser circulation also cause pulmonary arteriosclerosis. These include mitral stenosis, intra-auricular septal defects, chronic pulmonary infections and the several conditions mentioned in the preceding section. Diffuse vascular sclerosis

of the medium and smaller sized branches so called hyperplastic arteriolar sclerosis may be associated with hypertension of the lesser circulation syphilis rheumatic fever or it may be present without any apparent cause In the case of the last mentioned there is an increasing body of opinion to support the belief that the unexplained sclerosis is related to an essential form of hypertension of the lesser circulation

Primary pulmonary sclerosis without antecedent lung or heart disease has attracted particular attention because the condition may give rise to a characteristic clinical syndrome so called Ayer's disease This disease occurs most often in the syphilitic although syphilis is not the sole cause The patient with Ayer's disease is cyanotic as a result of the accompanying anoxemia but has comparatively little dyspnea Sooner or later edema sets in as well as other evidence of right heart failure The condition has been described in detail by Brenner and more recently reviewed by Leopold Brill and Krvgier analyzed twenty instances including one of their own The signs and symptoms do not differ significantly

from those occurring in other types of chronic cor pulmonale

The chest x ray findings in pulmonary arterio sclerosis are referable chiefly to the hypertension of the lesser circulation which usually coexists There is accentuation of the pulmonary conus and prominence of the hilar vascular markings In rare instances one can discern distinct sclerotic changes in the vessel walls The secondary polycythemia usually accompanying the condition does not produce demonstrable changes in the chest x rays unless there is pulmonary infarction Since it may be difficult at times to differentiate polycythemia vera from secondary polycythemia Hirsch also Hodes and Griffith have drawn attention to the fact that in the former one may encounter discrete spherical lesions involving especially the middle zones of the lungs whereas in the secondary form there is more apt to be hyperillumination of both lung fields and an accentuation of the hilar vascular markings Chapter 5 which deals with the pulmonary manifestations of blood disorders contains additional comment on the subject

Pulmonary Congestion and Edema

PHYSIOLOGICAL CONSIDERATIONS

In the presence of left ventricular failure if the cardiac venous inflow and right ventricular function remain adequate pulmonary congestion occurs which sooner or later leads to edema The high capillary pressure stasis and anoxia are important elements in the transudation of fluid in the lung In slow blood flow the active factors are also chemical in nature Once the activity of the several factors reaches a certain critical point edema can progress with great rapidity often with fatal results Hayward found that pulmonary edema does not occur unless the left atrial and pulmonary capillary pressures exceed the effective plasma osmotic pressure by a considerable margin In addition to high capillary pressure possibly a neurogenic factor may suddenly increase the capillary permeability A vicious cycle is established between the low intrathoracic pressure which serves to increase the pulmonary congestion and the hyperventilation

caused by dyspnea which further lowers the intrathoracic pressure (Drinker)

The transudation of fluid through the damaged capillary walls into the alveoli and the whipping up of this fluid into froth by respiratory activity cause increasing obstruction of the small air passages impede gas exchange and results in asphyxia The dyspnea cyanosis and bubbling rales of acute pulmonary edema are readily explained on the basis of this mechanism In the initial stages the condition is reversible In chronic heart failure changes take place in the alveoli which become thickened and rigid by the deposition of collagen According to Hayward the fact that acute pulmonary edema does not necessarily occur in spite of high pulmonary capillary pressure suggests either that the fluid is hindered in its escape into the interstitial tissue of the lung and air passages by the structural changes in the capillary walls and alveolar epithelium or that it is rapidly removed by the pulmonary lymphatic system

CLINICAL FEATURES

The causes of pulmonary congestion and edema are many and varied. The major ones are left ventricular failure secondary to hypertension of the greater circulation also coronary artery disease with myocardial infarction and valvular disease of the heart. In an analysis of 500 autopsies Cameron found that hypertensive heart disease, excluding chronic nephritis showed an incidence of pulmonary edema in 86 per cent, chronic nephritis 74 per cent, complete coronary obstruction 68 per cent, mitral stenosis, 65 per cent, and almost equally high percentages associated with cerebral hemorrhage, fractured skull, multiple fractures without cerebral hemorrhage, and pulmonary embolism. Additional causes are irritating gases neurogenic disturbances, excessive or rapid parenteral administration of fluid as well as rapid paracentesis (Figures 61A and B).

A comprehensive discussion of the clinical features of pulmonary congestion and edema is beyond the scope of this book. Suffice it to mention that the initial manifestations of left ventricular failure are usually referable to the lungs. The passive congestion and recurring episodes of acute pulmonary edema lead to various gradations of dyspnea ranging from mild shortness of breath after exertion to Cheyne Stokes respiration. In time, persistent cough expectoration and occasionally pain in the chest are caused by the resulting chronic pneumonitis and intercurrent infections, the congested lungs favoring the occurrence of the latter. In addition there are symptoms and signs referable to the failing heart itself.

With increasing cardiac decompensation exertional dyspnea comes on with the slightest effort so that soon the shortness of breath is present even when the individual is at rest. The dyspnea associated with a failing left ventricle characteristically occurs in paroxysms especially

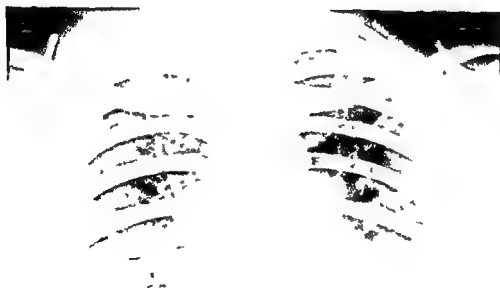
when the individual is recumbent, at which time the engorgement of the pulmonary circulation is greater. The individual is aroused during sleep by a seizure of cough, wheezing respiration and considerable distress, a condition commonly referred to as "cardiac asthma." Severe seizures are associated with cyanosis, tachypnea, audible rales, expiratory dyspnea and expectoration of frothy, pink stained sputum indicative of pulmonary edema. Unless one is aware of the patient's cardiac status and previous state of health, cardiac asthma may be mistaken for bronchial asthma and treated injudiciously with epinephrine and other bronchodilators instead of morphine and its analogues which are effective drugs for the condition.

ROENTGENOLOGY

Until recently the preclinical phenomena associated with pulmonary congestion and edema occupied the attention chiefly of physiologists and pathologists. The physician saw only the late stages of the disease. With greater use of roentgenography, the problem is assuming increasing clinical interest. Inasmuch as pulmonary congestion in its initial stages is transient and symptomless and, in advanced stages, the patient is apt to be too ill to stand a painstaking examination the use of roentgenography, particularly in routine hospital admissions has been of inestimable value in enlarging the understanding of this condition.

The roentgen features of pulmonary engorgement and edema are related to disturbances in cardiopulmonary dynamics, mentioned earlier in the chapter. Simple engorgement of pulmonary blood vessels without significant transudate in the alveoli is revealed in an accentuation of the hilar vascular shadows and of the adjacent lung markings. The appearance of the congested lungs varies depending on whether the condition is acute or chronic and on the presence or absence of associated lung and pleural changes.

Figure 61 Acute pulmonary congestion and edema after rapid intravenous instillation of 2500 cc of 5 per cent glucose in saline. A (Upper) Diffuse ground glass cloudiness of both lungs chiefly the right. (Patient admitted with abdominal pain, chill and fever. Operated on for an acute pelvic abscess. Continued high temperature and shortness of breath at the time chest x ray was taken.) B (Lower) One week later almost complete resolution of the opacity.



(See legend on opposite page)

In acute left ventricular failure, pulmonary edema manifests itself in a diffuse "butterfly" or "bat's wing" cloudiness of the central portions of the lungs, the opacity extending laterally from the hilar regions (Figures 62A and B). The "butterfly" appearance takes its descriptive from the, more-or-less, symmetrical, perihilar, confluent densities with irregular margins which characterize the lesions and the surrounding offset of translucent apical, basal and lateral zones. The "butterfly" shadows, encountered in acute pulmonary edema, do not depend on any specific changes in the tissues, rather on the fact that the lesions are concentrated in the medulla or interior portions of the lungs, as suggested by Herrin, Heiser and Hinson.

Gould and Torrance devised the following classification of pulmonary edema from the viewpoint of the roentgenologic-morphologic features (Table 6).

TABLE 6

MORPHOLOGIC CLASSIFICATION OF PULMONARY EDEMA

Type I	Central edema. Large confluent or even homogeneous dense, central or perihilar opaque shadows usually forming symmetrically bilateral densities giving the so called butterfly or bat's wing appearance.
Type II	Diffuse edema. Patchy, ill defined usually bilateral densities variable in size and distributed in a diffuse fashion. These shadows are frequently of varying density.
Type III	Focal edema. <ul style="list-style-type: none"> (a) Lobar dense, homogeneous consolidation bounded by a major fissure or fissures predominantly lobar in distribution. (b) Pseudosarcoma. One or more isolated large rounded discrete shadows resembling primary or metastatic tumor.

From Gould and Torrance. *Am J Roentgenol*, 73:366, 1955.

Azotemia with Pulmonary Manifestations

ETIOLOGIC CONSIDERATIONS

Because of unusual interest expressed on the subject, the pulmonary lesions occasionally found in the presence of azotemia will receive special consideration. Basically, however, the mechanism is the same as that underlying acute pulmonary edema. As in the latter, the primary cause of the pulmonary lesions in azotemia is left ventricular failure and fluid retention. The degree of elevation of the nitrogenous products in the blood does not parallel the lung changes and in extrarenal azotemia, without hypertension lung changes are not observed. Furthermore, experimental ligation of the ureters in animals thereby inducing death of uremia, is usually not associated with abnormal roentgen changes in the lungs unless the animals are also subjected to fluid infusion (Olsson).

There are some grounds for the belief that in cardiorenal disease associated with azotemia, an increase in capillary permeability, due to excess nitrogenous products in the blood, may be a contributing element in the lung changes. Hopps and Wissler found that the lesions of "uremic pneumonitis" may occur with little or no clinical

or pathologic evidence of left heart failure. In their experience, the development of pulmonary lesions was more readily correlated with the degree of acidosis, as judged by the depression in blood CO_2 combining power.

Hayward recognizes a subacute form of pulmonary edema occurring in uremia, malignant hypertension, acute nephritis, in occasional cases of polyarteritis nodosa and in association with the "rheumatic" lung in acute rheumatism. The condition is characterized by clotting and organization of the interstitial and alveolar exudate and is probably caused by a combination of left ventricular failure and altered capillary permeability. The pathological, clinical and roentgenological changes are identical in the several conditions mentioned. The scarcity of adventitious sounds in the lungs is explained by the organization of alveolar exudate which has a high fibrin content.

The so called "azotemic lung" is a heavy, firm voluminous organ, partly or wholly covered by a fibrous pleurisy. Microscopic examination reveals an irregular distribution of intra-alveolar fibrous or albuminous exudate, thickening of alveolar septa and a mononuclear cell reaction.

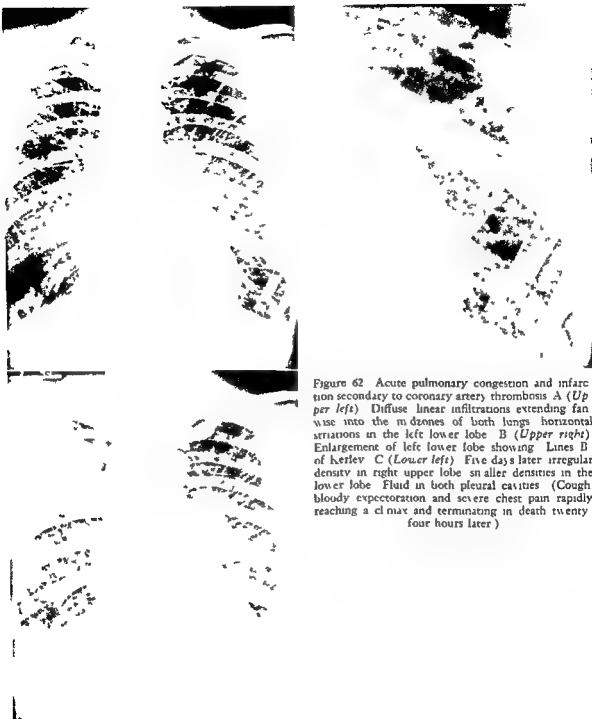


Figure 62 Acute pulmonary congestion and infarction secondary to coronary artery thrombosis A (*Upper left*) Diffuse linear infiltrations extending fanwise into the midzones of both lungs horizontal striations in the left lower lobe B (*Upper right*) Enlargement of left lower lobe showing Lines B of Kerley C (*Lower left*) Five days later irregular density in right upper lobe smaller densities in the lower lobe Fluid in both pleural cavities (Cough bloody expectoration and severe chest pain rapidly reaching a climax and terminating in death twenty four hours later)



Figure 61. Azotemia with pulmonary lesions. A (Left) Enlarged heart. B (Right) Nine months later all defined irregular densities extending fanwise into mid and upper lung fields; pleural reaction at bases. (Hypertensive cardiovascular disease, admitted in severe uremia; autopsy showed marked pulmonary edema, hemorrhage and possibly uremic infarcts; hypertensive heart disease, contracted kidneys.) (From Rubin: *Diseases of the Chest*, W. B. Saunders Co.)

The capillaries are engorged with red cells. The alveolar ducts are often prominent, showing a pseudomembrane which also lines the alveoli. Depending also on associated cardiac disease, there are patches of hemorrhage throughout the organ and often areas of infarction. In addition, one finds evidence of renal disease.

ROENTGENOLOGY

The chest x-ray reveals uneven mottling extending from the hilar regions into the adjacent portions of the lung, obscuring the normal root shadows. The distribution is fanwise, the periphery, apices and bases of the lungs being spared (Figure 63). The conglomeration of irregular densities in the midzonal portions of the lungs, surrounded by a fairly well illuminated zone of tissue, may be quite striking, especially in the absence of significant symptoms or signs referable to the chest. There are times when the x-ray appearance alone may be sufficiently impressive to

suggest the possible existence of azotemia and prompt the physician to investigate further for its presence. But as mentioned, the same roentgen configurations may be obtained in pulmonary edema caused by acute left ventricular failure without renal insufficiency. In some cases the changes are not widespread and may even be limited to one lung. Of 100 cases of pulmonary edema, Gould and Torrance found ninety with central edema, seven with diffuse edema and three with focal edema. Of the group with central edema, thirteen could be classified as pure uremic, i.e., those due to primary renal disease, and ten as uncomplicated uremic, i.e., renal failure secondary to other disease, usually advanced essential hypertension.

It is noteworthy that anaphylactic reactions occurring during drug sensitization or after blood transfusions with incompatible blood and associated with acute glomerulonephritis and pulmonary edema may produce roentgen changes in

the lungs or a type described above (Figure 64). In a study of the roentgenological and pathological findings in antigenic (azotemic) pneumonitis Sante and Wyatt cite the work of Trueta Prichard and their co workers with respect to the ischemia of the kidney after injection of bacterial toxin into the renal circulation thereby producing anuria. Sante and Wyatt speculate

that a similar mechanism might be at play under the influence of the same toxic agent and that the so called azotemic lung might also be due to ischemia of the parenchymal circulation of the lung. They suggest the more appropriate term antigenic pulmonary edema.

Three years later Prichard and co workers reported additional observations which would

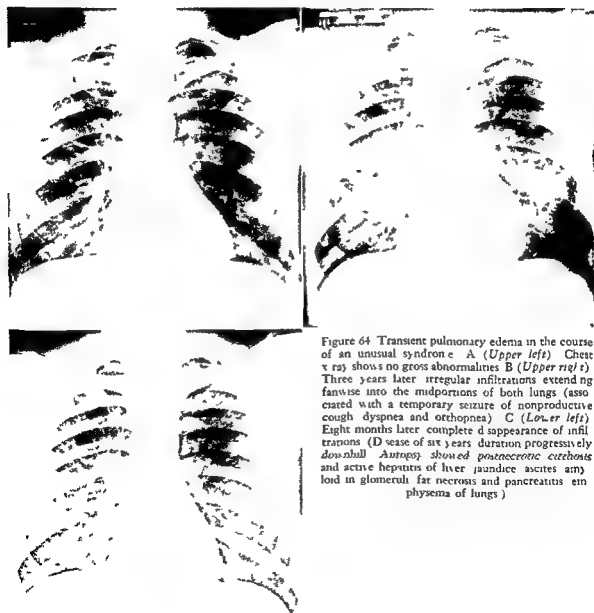


Figure 64 Transient pulmonary edema in the course of an unusual syndrome. A (Upper left) Chest x ray shows no gross abnormalities. B (Upper right) Three years later irregular infiltrations extending fanwise into the midportions of both lungs (associated with a temporary seizure of nonproductive cough, dyspnea and orthopnea). C (Lower left) Eight months later complete disappearance of infiltrations. (Disease of six years duration progressively downhill). Autopsy showed postnecrotic cirrhosis and active hepatitis of liver, jaundice, ascites, amyloid in glomeruli, fat necrosis and pancreatitis (emphysema of lungs).

seem to bear out the aforementioned speculations. In a series of angiographic experiments in animals these investigators were impressed with the frequency with which peripheral ischemia occurred in the midportions of the lungs. The chest x ray presented bat's wing shadows as noted in subacute pulmonary edema complicating left ventricular failure. These investigators suspect that the condition in man may be associated with a change in the distribution of the pulmonary blood flow such as that seen in their experimental animals. They found that blood can pass from the pulmonary arteries to the pulmonary veins into the deeper parts of the lung without circulating through the peripheral portion. This may give rise to the roentgen bat's wing shadows. Reference is also made to the angiographic studies of Goodwin and co workers who found that in patients with severe mitral stenosis and pulmonary hypertension there were indications of an occlusive process or spasm oc-

curing in the peripheral branches of the pulmonary arterial tree.

Following effective treatment of the failing heart the initial acute seizures of pulmonary edema are reversible and the chest x ray markings may assume their previous state. Olsson cites experiences with the use of the artificial kidney. In a series of sixteen cases treated by control of fluid balance signs of regression of the pulmonary edema were observed in all and in ten the changes disappeared completely. After recurring seizures and the establishment of a state of chronic pulmonary congestion the densities became more ill defined the picture changing also as a result of associated pulmonary infarction and low grade infection. The densities tend to gravitate to the bases of the lungs which may be obscured by free fluid in one or both pleural cavities. If one pleural cavity is involved it is more likely to be the right as is true of most cases of pleural transudates due to a failing heart.

Hydrothorax

Free fluid in the pleural cavity is not often seen during the initial transient seizures of acute pulmonary edema. In the presence of pulmonary infarction or left ventricular failure an effusion is often encountered especially in the right pleural cavity. The reason for the preponderance of right sided hydrothoraces in advanced heart failure has provoked considerable discussion. According to Dock the venous blood in the lungs must return to the left ventricle which has its center of mass near the ventral chest surfaces and the diaphragm slightly to the left of the midline. Because of the effect of gravity on this flow Dock estimates that the venous pressure at the bases expressed in its equivalent of water is 70 to 30 cm greater than that of the apex of subjects in the orthopneic position. When the patient is in the right recumbent position frequent with cardiac patients the venous pressure in the lateral and basal parts of the right lung is 10 to 20 cm higher than that in any part of the left lung. These factors he believes are of paramount importance in explaining the frequency of basal pulmonary edema and of right sided hydrothorax in cardiac failure since the forma-

tion of tissue fluid increases rapidly with the rise in venous pressure.

In studies by White and co workers also McPeak and Levine several explanations are given for the preponderance of right sided hydrothoraces in congestive heart failure which have many features in common. In addition to the anatomic and hydrostatic factors described by Dock it is pointed out that pulmonary lymphatic drainage takes place almost entirely through the right lymphatic duct so that in the presence of lymphatic stasis especially in the right lateral recumbent position capillary leakage is augmented. The nature of the heart condition does not seem to have any bearing on the side where the fluid accumulates. In a study by White and co workers fifteen cases showed unilateral right hydrothorax and thirteen showed unilateral left hydrothorax. Of the thirteen with left hydrothorax complete obliteration of the right pleural cavity was present in twelve and unilateral left pulmonary infarction in the remaining case. In contrast only four such complicating factors were present among the fifteen unilateral right hydrothoraces. In other words

if a left-sided hydrothorax is present, the reason the right side is spared is because there is no space for the accumulation of fluid in the right pleural cavity.

The chest x-ray findings in hydrothorax complicating cardiac disease do not differ from other types of pleural effusions. Of particular interest, from the view point of differential diagnosis, is the rare occurrence of a localized interlobar effusion which may simulate a "vanishing" tumor. The exact delineation of interlobar effusions requires lateral, oblique as well as postero-anterior projections. The encysted collection of fluid occurs with few exceptions in the horizontal fissure of the right lung. In two of five patients with such interlobar effusions, Weiss and co-workers found at autopsy that the cause of the localization of the fluid was due to an obliterative

pleurisy of part or all of the remaining pleural cavity. The presence of signs of cardiac decompensation, pulmonary congestion and the rapid disappearance of the mass after the institution of treatment, are major points in the differential diagnosis of loculated effusions from pulmonary neoplasms, pneumonias and other intrinsic diseases. Higgins and co-workers found reports of thirty-six well documented cases of interlobar pleural effusions due to congestive heart failure, and added six of their own, making a total of forty-two. Twenty-six were located in the right transverse fissure and another six in the right oblique fissure. These investigators believe that one of the reasons for the preponderance of right-sided loculations of fluid is because they are more readily discovered at this site in routine postero-anterior chest x-rays.

Cavernous Hemangioma of the Lung

CLINICAL FEATURES

In 1932, Reading reported the case of a patient who had cyanosis, digital clubbing and polycythemia associated with congenital telangiectasis of the lung. The patient died of a brain abscess. Four years later, Bowers reported the case of an infant with a pulmonary hemangioma who died of a fatal hemorrhage the second day after birth. These reports, published in state medical journals, escaped general notice until Rodes, in 1938, drew attention of the medical profession to the occurrence of cavernous hemangioma of the lung with secondary polycythemia. Following this report, increasing numbers of reports appeared in the literature. In 1949, Yuter, and Griffin reviewed the world literature and collected forty-five known cases. Five years later, Weiss and Gasul reviewed 149 case reports, including two of their own and three unpublished cases. The condition has been described under several terms: arteriovenous fistula, arteriovenous aneurysm, cavernous hemangioma and congenital telangiectasis of the lung.

Cavernous hemangioma of the lung is a congenital, at times, familial malformation closely allied to hereditary hemorrhagic telangiectasis (Osler) sometimes found in the skin, mucous

membranes and other organs. Baer and co-workers found that in 50 per cent of the reported cases of cavernous hemangioma of the lung other vascular abnormalities such as telangiectasis, capillary hemangiomas and spider nevi were exhibited. The cases reviewed by Weiss and Gasul included four in which numerous small arteriovenous fistulas were present rather than a single arterial dilatation. Moyer and Ackerman reported a family with hemorrhagic telangiectasis of which two members had pulmonary hemangiomas. The hereditary feature of the disease was exceptionally well illustrated in another family in which the mother and son had pulmonary fistulas and in another member a probable pulmonary fistula with rupture and death. Of thirty-six members of this family whose histories were available, seven had signs of hereditary hemorrhagic telangiectasis and an additional four persons may have been affected (Heyde).

The pulmonary defect consists of a collection of thin walled sacs made up of distended blood vessels. The resulting arteriovenous communication allows admixture of venous and arterial blood causing variable degrees of anoxia. The severity of the latter depends on the amount of unoxygenated blood passing through the fistula.

White estimates that approximately 30 per cent of the blood must be shunted before cyanosis becomes manifest in otherwise healthy individuals.

The symptoms and signs of cavernous hemangioma of the lung vary widely. The condition may be discovered accidentally in the course of a routine chest x-ray survey. In others, there may be signs of anoxia as evidenced in dyspnea, cyanosis, polycythemia, clubbing of digits, weakness, dizziness, fainting spells, headache, epileptic fits and transitory paralysis. Additional manifestations include hemoptysis and a bruit. Depending on the size of the arteriovenous communication there may or may not be cardiac enlargement. Following extirpation of the aneurysm there is a decrease in the size of the heart. Cavernous hemangioma of the lung may be mistaken for congenital heart disease and occasionally for polycythemia vera. Cases have been reported of cavernous pulmonary hemangioma in association with pulmonary artery, aortic septal defects and other malformations. Maier and co-workers reported an instance of bacterial endocarditis superimposed on an arteriovenous aneurysm.

ROENTGENOLOGY

The roentgen findings of cavernous hemangioma are fairly characteristic provided the possibility of the existence of the condition is kept in mind in patients showing one or more localized densities in the lung, the nature of which cannot be determined by conventional means, especially if evidence of anoxia is present. The hemangioma may appear as a compact group of small infiltrations presenting a "comet"-like appearance. More often, one sees several fairly large, irregular lobulated densities in the mid or lower portions of a lobe, the entire mass being connected to the hilar vessels by one or more linear bands. During fluoroscopy the density may be shown to vary in size with changes in intrathoracic pressures. This is accomplished in the following manner: With the mouth closed and the nostrils occluded, the patient is told to exhale (Valsalva maneuver) and then to inhale (Müller's maneuver). By these maneuvers the intrapleural pressure is first raised and then

lowered thereby causing a decrease and then an increase in the size of the mass.

Sectional roentgenography and angiocardiology, especially the latter, are decisive in delineating a pulmonary hemangioma and its vascular connection with the hilar blood vessels. In a series of nine cases, Steinberg and McClenahan found the classical symptomatology in only one. In three instances, the patients had no symptoms, in two the pulmonary arteriovenous fistula was an incidental finding and, in the remaining two, acute cerebral conditions were the presenting symptoms. These investigators believe that the diagnosis of arteriovenous fistula can often be made by conventional roentgenography if the index of suspicion is high. The diagnosis is established by angiocardiology.

In 1939, Smith and Horton described the first case of pulmonary hemangioma in which a diagnosis was made clinically. In recent years the diagnosis has been made quite often and confirmed by operation. Shenstone is credited with the first successful pneumonectomy for the removal of a cavernous hemangioma. The case had been previously diagnosed by Hepburn and Dauphinee. Of the total of sixty-six reported cases, slightly more than half have been treated surgically, the majority successfully. The following case is reported through the courtesy of Dr Alfred Goldman.

Case 31. Male—Age 26

In 1939 the patient was examined by a physician and he was told that he might have leakage of a heart valve. A chest film revealed no abnormalities. In 1942 the patient was rejected by the Army during the course of a routine preinduction examination because of a shadow in the left lung. About this time the patient began to note clubbing of the fingers and cyanosis of the nail beds and lips at first present only on exertion but which soon became constant. Later the patient developed frequent nose bleeds. Two months prior to admission to the hospital the patient was in an altercation and suffered an injury to the face. During the course of his hospitalization due to this injury, the patient had a chest film taken and he was found to have a lesion in his left upper lung field also a murmur in the left chest and other findings consistent with

the presence of an arteriovenous shunt. It was because of this that the patient entered Barnes Hospital for further treatment and diagnosis.

Physical examination on admission disclosed a marked plethora to the face, cyanosis of the mucous membranes, marked clubbing of the fingers and toes with a cyanotic hue to the nailbeds. A few hemangiomas were noted over the face and on the anterior and posterior aspects of the chest. The lungs were clear to percussion and auscultation. The heart did not appear to be enlarged and there was a normal sinus rhythm. There was a loud rumbling grade 3 pre-systolic murmur heard at the apex, transmitted laterally and into the back. This was associated with a mild diastolic component. The second pulmonary sound was considerably louder than the aortic second sound. The abdomen was negative. The routine laboratory data revealed normal urinalysis. The red blood count was 6.7 million with 21 grams of hemoglobin and the white blood count was 7,350 cells with a normal differential. The red blood cells and platelets appeared normal. The blood type was group O RH positive. The ECG was interpreted as being normal.

A ray examination of the chest, including routine lymphography, revealed a roundly lobulated density in the left midlung field measuring 5 by 5 centimeters. There were numerous areas of radiolucency within the density and demonstrated by laminagraphy. Medial to the mass there were several large pulmonary vessels leading from the left hilum directly toward the medial border of the mass (Figures 65A, B and C). There were marked pulsations at the medial border of the mass and almost no pulsations on its lateral border, suggesting the possibility of arterial pulsations medially and the venous channels laterally. Intravenous angiocardiography was carried out using 50 cc of 50 per cent diodrast in the right antecubital vein. The dye was seen to pass through the branches of the left pulmonary

artery into the round lobulated mass noted previously in the left midlung field. There was a puddling of dye in this area (Figure 65D). The collection of abundant dye in the rounded shadow with evidence of both arterial and venous bloods indicated an arteriovenous aneurysm. No other abnormalities were noted.

On August 16, 1950 a left exploratory thoracotomy was carried out and a mass measuring about 8 x 5 cms was found in the pectoral segment of the left upper lobe over which a possible thrill could be elicited. There was marked superficial collateral circulation in the region of the mass as well as overlying the pericardium and mediastinum. The fissure between upper and lower lobes was well identified and accordingly with little or no difficulty a left upper lobectomy was carried out which completely excised the mass and caused a marked reduction in the remaining pulmonary vessels in the hilar region. No more thrill was palpable after removal of the left upper lobe. The patient did exceptionally well postoperatively. The removed specimen was reported as a left upper lobe of the lung containing an arteriovenous fistula. All efforts were made to keep this patient well hydrated postoperatively and after the second postoperative day the patient was able to take all necessary fluid by mouth without parental aid. The wound healed per primam. On the first postoperative day the hemoglobin had dropped to 18 gms, the red blood count to 5.5 million. By the third postoperative day the hemoglobin had dropped to 13.2 gms. Associated with this reduction in the polycythemia there was also noted a marked regression in the previously noted cyanosis of the mucous membrane. No change was noted in the clubbing of the digits. The patient was discharged on the twelfth postoperative day. The discharge diagnosis was arteriovenous fistula of the left upper lobe and hereditary hemorrhagic telangiectasia.

Pulmonary Embolism and Infarction

Although thromboembolism and infarction are part of the same basic disturbance and often described under one heading the two are not synonymous since thromboembolic phenomena need not necessarily be associated with lung lesions. In practice, however, the symptoms which often alert one to the presence of the vascular disturbance are those referable to the pulmonary infarction. Pulmonary artery thrombosis in situ

is rare and the effects of such blood vessel obstruction are clinically indistinguishable from embolization arising in the heart or the venous system.

ETIOLOGIC CONSIDERATIONS

Pulmonary embolism is increasing in frequency. The condition is likely to grow in importance as the population ages. Various theories

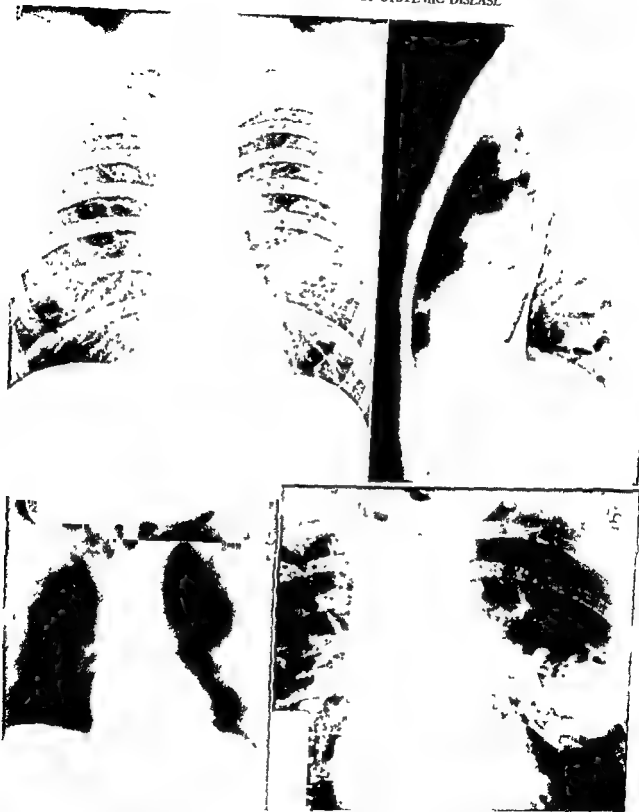


Figure 65 Case 31 Cavernous hemangioma of lung A, B and C (Upper left and right, lower left) Rounded, lobulated density in left midlung, indistinct connections with hilar structures D (Lower right) Angiocardiography reveals dye in lobulated mass, also dye filled channels communicating with hilar vessels (Courtesy, Dr Alfred Goldman, St Louis, Mo)

have been proposed to explain the increasing incidence of the disorder including such factors as the large number of elderly persons being subjected to major operations and the mounting number of victims to industrial and automobile accidents. These several causes and the prolonged bed confinement which the injuries entail favor stasis of the venous circulation thrombosis and embolism.

It has been estimated that pulmonary embolism is found in approximately 75 per cent of necropsy material and causes 6 per cent of all postoperative deaths. The incidence of pulmonary embolism depends to a large extent on the nature of the material studied. Towbin surveyed the incidence of pulmonary embolism in an elderly institutional population including 517 cases examined at autopsy. The study brought out the importance of age, sex and periods of enforced rest. A greater incidence was found among women. Of the 517 cases examined at autopsy, thromboembolic lesions were present in the lungs in 137 or 25.7 per cent. In those seventy years of age or over embolism was present in the lungs in 34 per cent. Fowler and Bollinger also found fatal pulmonary emboli to occur most commonly among patients with medical gynecologic, genitourinary and general surgical services in that order and rarely in obstetric cases. The most common predisposing factors found were cardiac disease, venous thrombosis, dehydration and immobilization. These investigators found in their study the heart to be the site of origin in 57.8 per cent and venous thrombosis in 47.7 per cent of all the fatal cases.

The close relationship existing between disease of the veins especially those of the lower extremity and embolism is well known. Thrombophlebitis of superficial veins rarely gives rise to serious complications for the reason that the local reaction in the wall of the vein. The lowest incidence of emboli occurs in migratory phlebitis in which the lesions are limited to small superficial veins the disease being largely perivascular. On the other hand, quiet thrombosis or so-called phlebothrombosis in which the infectious element and the damage to the vessel wall are

considerable is much more dangerous because the loosely attached clot is able to float away in the blood stream and enter the heart and lungs. In the absence of heart disease nearly all emboli arise from blood clots in the deep veins of the legs. Thrombosis of the veins of the upper extremities, head, neck and trunk seldom leads to embolism. This is supported by the statistics of Barler and his associates also of Henderson. The latter studied 189 cases of pulmonary embolism. In 86 per cent the sources of embolization were found in thrombosed veins which were direct or indirect tributaries of the lower third of the vena cava.

In the case of emboli originating from thrombi in the right side of the heart there is almost invariably present congestive heart failure and often auricular fibrillation. Occasionally the thrombus is at the site of a myocardial infarct involving the lateral wall or septum of the right ventricle. Mural thrombi in the right side of the heart are a more frequent source of emboli to the lungs than is generally appreciated. Approximately one third of adults who die of heart disease are found to have mural thrombi at autopsy. The differential diagnosis between acute pulmonary infarction and myocardial infarction is often a difficult one to make. The two may coexist. In the absence of a clear cut history any acute seizure characterized by severe chest pain, dyspnea and tachycardia is apt to be ascribed to acute coronary artery disease and myocardial infarction. This is probably the main reason why pulmonary embolism and infarction are so often misdiagnosed.

CLINICAL FEATURES

A blood clot in a pulmonary artery whether caused by a thrombus within the vessel or more often by an embolus from a distant site is one of the dreaded complications of medical and surgical practice. The classical seizure occurs in elderly or overweight individual who had recently undergone a major pelvic or abdominal operation. A week or ten days after the operation the patient is suddenly seized with severe chest pain, dyspnea, cyanosis, tachycardia, faintness, sweating, vomiting and shock. Death may

occur almost instantaneously or after a lapse of a few hours. The classical picture is the exception rather than the rule. With increasing familiarity with the condition it is possible to differentiate subacute and chronic forms of the disease. The latter assume various disguises depending on the nature of the associated pulmonary infarction and bronchopneumonia.

The pulmonary infarction which follows embolism gives rise to a train of symptoms and signs which reflect the injury the lung sustains. There is cough, hemoptysis, fever, chest pain and leukocytosis. The patient may become jaundiced as a result of increase in bile pigment from the extravasated blood in the affected lung which the congested liver is unable to handle. The physical signs are characterized by exquisite tenderness of the chest over the affected part of the lung, possibly a friction rub and evidence of lung consolidation. Free fluid in the pleural cavity is often present.

In spite of an imposing number of symptoms and signs which may be encountered in the presence of pulmonary embolism and infarction or possibly *because* of the abundance of such signs few conditions are diagnosed incorrectly as often as pulmonary embolism and infarction. The disease has been aptly termed 'the great deceiver' (Wright and Foley). Miller and Berry in an analysis of 104 fatal cases of pulmonary embolism and infarction noted that in only forty four cases was the disease correctly diagnosed. In the remainder the clinical diagnosis recorded as the cause of death included congestive heart failure (14), myocardial infarction (6), pneumonia (6), bronchogenic carcinoma (5) and several other conditions. In fourteen no diagnosis was made. These investigators also draw attention to the fact that the typical picture of pulmonary embolism and infarction is the exception rather than the rule.

Owen and co-workers reported twelve cases of chronic cor pulmonale and heart failure as a result of multiple and for the most part silent pulmonary emboli. Postmortem study revealed the role of widespread organized embolization of the lungs as the only etiologic factor responsible in these patients. The study included twelve

such cases over a period of twenty years indicating that it is a rare occurrence although the figures are somewhat misleading because the material was selected in order to present the purest form of the syndrome. In each patient the dyspnea and cough antedated the appearance of cardiac hypertrophy and congestive heart failure the latter being the cause of death in every case. The diagnosis was usually unsuspected. The authors believe that a large proportion of cases of so-called Ayerza's syndrome result from latent embolization of the lung.

ROENTGENOLOGY

Much has been written on the electrocardiographic changes accompanying embolism especially in cases in which there is sufficient interference with the pulmonary circulation to cause acute cor pulmonale. Comparatively little has been written on the chest x-ray findings probably because events occur so rapidly that adequate roentgen examinations are seldom obtainable and when chest x-rays are taken the bedside product is of such poor quality as to preclude an adequate definition of detail. As mentioned previously pulmonary embolism does not always result in infarction of lung tissue. This applies especially to large emboli which lodge in a major pulmonary artery, death occurring so suddenly that there is no time for secondary effects to register in the lungs. Occasionally if the patient lives long enough and it is possible to obtain readable films the chest x-ray may reveal features of unusual interest.

In 1938 Westermarck described certain roentgen findings in lung embolism without infarction which he believed were of diagnostic significance. The findings consist of ischemia of the affected lung which reveals itself in a well defined clear zone on the peripheral side of the embolus with diminished or absent vascularization of the part. The diminished vascular structure is reflected in an increased radiability of the lung. As a result of the distribution of the arterial branches the zone of increased radiability assumes the shape of a wedge with its apex directed toward the hilum and its base toward the periphery of the lung. The shape of the wedge

is best seen in the lateral and oblique projections Shapiro and Rigler reported three cases of pulmonary embolism, confirmed at autopsy, which substantiated Westermarck's findings. Others have been unable to demonstrate such changes.

If more precise information were available of the roles played by the pulmonary and bronchial arteries in disease, a satisfactory explanation might be at hand for the contradictory statements of observers relative to the incidence of pulmonary infarction following embolism. As indicated in the preceding chapter, the bronchial arteries probably play a minor role in health. But, under abnormal conditions, the bronchial arteries may assume certain functions of the pulmonary arteries, as witness the collateral circulation which quickly becomes established between the two systems.

Ellis and co-workers found that the nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed. They believe that the bronchial arterial circulation is not necessary for this purpose. In fact they found that the bronchial arterial circulation may actually be a contributing factor to the development of pulmonary infarction after pulmonary embolism since the hemorrhage that occurs into the pulmonary tissue, after pulmonary embolism, may come from the bronchial arterial circulation. On the other hand Kjellberg and Olsson claim that the reason for the rarity of finding chest x-ray evidence of pulmonary embolism without infarction lies in the fact that no roentgenological changes are observed in the lungs if the circulation through the bronchial artery to the part is undisturbed.

In the "typical" case, pulmonary infarction

is characterized roentgenologically by a wedge shaped shadow of homogeneous density in one of the lower lobes (Figure 66). At first the shadow is diffuse but after organization it assumes a more homogeneous appearance with sharply demarcated margins. It should be emphasized, however, that the "typical" chest x-ray, like the "typical" clinical picture, is the exception rather than the rule. In their basic contributions to the subject, Hampton and Castleman have drawn attention to a "hump" sized upper margin of tissues occasionally seen when a costophrenic angle is involved. In the process of healing, the infarcts may cast transverse, linear densities (Fleischner lines) which may be confused with "septal" lines or interlobar pleurisy. The diversity of x-ray findings are such that a differential diagnosis is often difficult to make unless one suspects the existence of the condition on the basis of the history and clinical findings, especially the presence of a potential nidus from which an embolism might originate.

In most cases a pulmonary infarct presents a picture of bronchopneumonia, obscured by fluid. In an analysis of the chest x-ray findings of fifty patients with pulmonary embolism and infarction, confirmed at autopsy, Miller and Berry found that only seven showed findings compatible with pulmonary infarct. Ten cases were read as pneumonias, seven as congestion, five as pleural effusion, ten as parenchymal abnormalities of one type or another and in eleven the findings were within "normal" limits. Among the uncommon sequelae of pulmonary infarction which may reveal unusual chest x-ray findings are aseptic necrosis and cavitation of the lung due to bland emboli and, on rare occasion, septic pulmonary infarction.

Bibliography

PHYSIOLOGICAL DISTURBANCES, PULMONARY HYPERTENSION, PULMONARY ARTERIOSCLEROSIS

BRENNER O. Pathology of the Vessels of the Pulmonary Circulation. *Arch Int Med* 56:711-457, 724-976, 1189-1935.

BRIEL I. C. and KRYGIER J. J. Primary Pulmonary Vascular Sclerosis. *Arch Int Med* 68:560, 1941.

BRYNTO W. D. Primary Pulmonary Hypertension. *Brit Heart J* 12:305, 1950.

CAMERON G. H. Pulmonary Edema. *Brit Med J*, 1-1965, 1949.

CARMICHAEL J. H. E. Personal Communication 1954.

CARMICHAEL J. H. E., JULIAN D. G., JONES G. P. and WREN E. M. Radiological Signs in Pulmonary Hypertension. *Brit J Radiol* 27:393, 1954.

occur almost instantaneously or after a lapse of a few hours. The clinical picture is the exception rather than the rule. With increasing familiarity with the condition it is possible to differentiate subacute and chronic forms of the disease. The latter assume various disguises depending on the nature of the associated pulmonary infarction and bronchopneumonia.

The pulmonary infarction which follows embolism gives rise to a train of symptoms and signs which reflect the injury the lung sustains. There is enough hemoptysis, fever, chest pain and leukocytosis. The patient may become jaundiced as a result of increase in bile pigment from the extravasated blood in the affected lung which the congested liver is unable to handle. The physical signs are characterized by exquisite tenderness of the chest over the affected part of the lung, possibly a friction rub and evidence of lung consolidation. Free fluid in the pleural cavity is often present.

In spite of an imposing number of symptoms and signs which may be encountered in the presence of pulmonary embolism and infarction or possibly because of the abundance of such signs few conditions are diagnosed incorrectly as often as pulmonary embolism and infarction. The disease has been aptly termed the great deceiver (Wright and Foley). Miller and Berry in an analysis of 104 fatal cases of pulmonary embolism and infarction noted that in only forty-four cases was the disease correctly diagnosed. In the remainder the clinical diagnosis recorded was the cause of death, included congestive heart failure (14), myocardial infarction (6), pneumonia (6), bronchogenic carcinoma (5) and several other conditions. In fourteen no diagnosis was made. These investigators also draw attention to the fact that the typical picture of pulmonary embolism and infarction is the exception rather than the rule.

Owen and co-workers reported twelve cases of chronic cor pulmonale and heart failure as a result of multiple and for the most part silent pulmonary emboli. Postmortem study revealed the role of widespread organized embolization of the lungs as the only etiologic factor responsible in these patients. The study included twelve

such cases over a period of twenty years indicating that it is a rare occurrence, although the figures are somewhat misleading because the material was selected in order to present the purest form of the syndrome. In each patient the dyspnea and cough antedated the appearance of cardiac hypertrophy and congestive heart failure, the latter being the cause of death in every case. The diagnosis was usually unsuspected. The authors believe that a large proportion of cases of so-called Ayer's syndrome result from latent embolization of the lung.

ROENTGENOLOGY

Much has been written on the electrocardiographic changes accompanying embolism especially in cases in which there is sufficient interference with the pulmonary circulation to cause acute cor pulmonale. Comparatively little has been written on the chest x-ray findings probably because events occur so rapidly that adequate roentgen examinations are seldom obtainable and when chest x-rays are taken the bedside product is of such poor quality as to preclude an adequate definition of detail. As mentioned previously, pulmonary embolism does not always result in infarction of lung tissue. This applies especially to large emboli which lodge in a major pulmonary artery, death occurring so suddenly that there is no time for secondary effects to register in the lungs. Occasionally if the patient lives long enough and it is possible to obtain readable films the chest x-ray may reveal features of unusual interest.

In 1938 Westerman described certain roentgen findings in lung embolism without infarction which he believed were of diagnostic significance. The findings consist of *ischemia* of the affected lung which reveals itself in a well defined clear zone on the peripheral side of the embolus with diminished or absent vascularity of the part. The diminished vascular structure is reflected in an increased radiability of the lung. As a result of the distribution of the arterial branches, the zone of increased radiability assumes the shape of a wedge with its apex directed toward the hilum and its base toward the periphery of the lung. The shape of the wedge

is best seen in the lateral and oblique projections Shapiro and Rigler reported three cases of pulmonary embolism, confirmed at autopsy, which substantiated Westermark's findings. Others have been unable to demonstrate such changes.

If more precise information were available of the roles played by the pulmonary and bronchial arteries in disease, a satisfactory explanation might be at hand for the contradictory statements of observers relative to the incidence of pulmonary infarction following embolism. As indicated in the preceding chapter, the bronchial arteries probably play a minor role in health. But, under abnormal conditions the bronchial arteries may assume certain functions of the pulmonary arteries, as witness the collateral circulation which quickly becomes established between the two systems.

Ellis and co workers found that the nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed. They believe that the bronchial arterial circulation is not necessary for this purpose. In fact, they found that the bronchial arterial circulation may actually be a contributing factor to the development of pulmonary infarction after pulmonary embolism since the hemorrhage that occurs into the pulmonary tissue, after pulmonary embolism, may come from the bronchial arterial circulation. On the other hand, Kjellberg and Olsson claim that the reason for the rarity of finding chest x-ray evidence of pulmonary embolism without infarction lies in the fact that no roentgenological changes are observed in the lungs if the circulation through the bronchial artery to the part is undisturbed.

In the 'typical' case pulmonary infarction

is characterized roentgenologically by a wedge shaped shadow of homogeneous density in one of the lower lobes (Figure 66). At first the shadow is diffuse but after organization it assumes a more homogeneous appearance with sharply demarcated margins. It should be emphasized, however, that the 'typical' chest x-ray, like the 'typical' clinical picture, is the exception rather than the rule. In their basic contributions to the subject, Hampton and Castleman have drawn attention to a "hump-sized upper margin of tissues occasionally seen when a costophrenic angle is involved. In the process of healing the infarcts may cast transverse, linear densities (Fleischner lines) which may be confused with 'septal' lines or interlobar pleurisy. The diversity of x-ray findings are such that a differential diagnosis is often difficult to make unless one suspects the existence of the condition on the basis of the history and clinical findings, especially the presence of a potential nidus from which an embolism might originate.

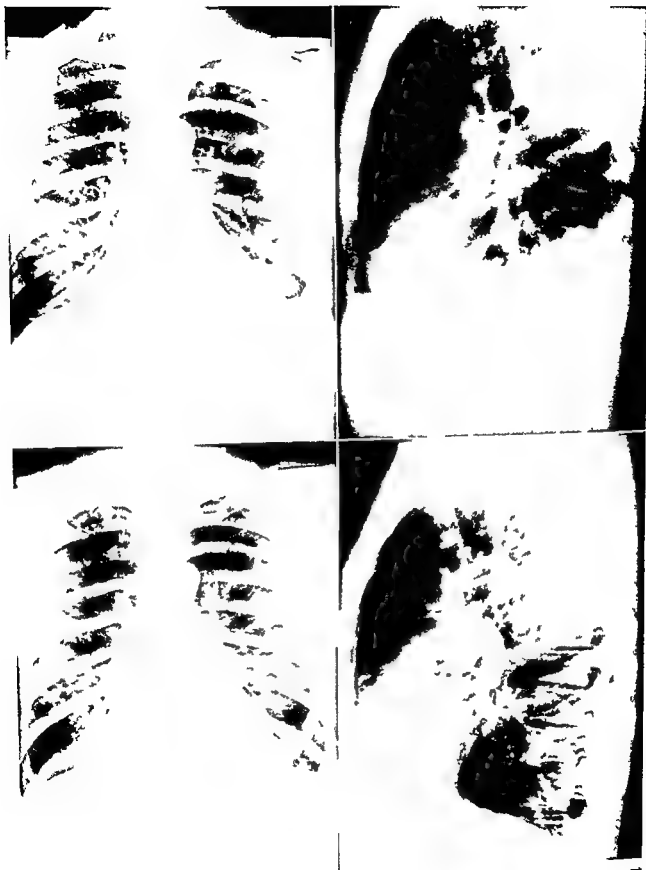
In most cases a pulmonary infarct presents a picture of bronchopneumonia, obscured by fluid. In an analysis of the chest x-ray findings of fifty patients with pulmonary embolism and infarction confirmed at autopsy, Miller and Berry found that only seven showed findings compatible with pulmonary infarction. Ten cases were read as pneumonias, seven as congestion, five as pleural effusion, ten as parenchymal abnormalities of one type or another and in eleven the findings were within "normal" limits. Among the uncommon sequelae of pulmonary infarction which may reveal unusual chest x-ray findings are aseptic necrosis and cavitation of the lung due to bland emboli and, on rare occasion, septic pulmonary infarction.

Bibliography

PHYSIOLOGICAL DISTURBANCES, PULMONARY HYPERTENSION, PULMONARY ARTERIOSCLEROSIS

- BRENNER, O. Pathology of the Vessels of the Pulmonary Circulation. *Arch Int Med* 56:211-457, 724-976, 1189-1935.
 BRILL, I. C., and KRYGER, J. J. Primary Pulmonary Vascular Sclerosis. *Arch Int Med* 68:560-1941.

- BRINTON, W. D. Primary Pulmonary Hypertension. *Brit Heart J* 12:305-1950.
 CAMERON, G. R. Pulmonary Edema. *Brit M J*, 1965, 1949.
 CARMICHAEL, J. H. E. Personal Communication 1954.
 CARMICHAEL, J. H. E., JULIAN, D. G., JONES, G. P., and WREN, E. M. Radiological Signs in Pulmonary Hypertension. *Brit J Radiol* 27:393-1954.



(See legend on opposite page)

PULMONARY MANIFESTATIONS OF CARDIOVASCULAR

CONCORDANCE

Circulation Foreign Letters *JAMA*, 149 1485 1957
 DUFFY L G GORDON J F, STINER R F, and VAN
 LERVEN B D The Clinical and Radiological Assessment
 of the Pulmonary Arterial Pressure in Mitral Stenosis
Brit Heart J, 15 393 1953
 DUNN D T, SCHULTZ M and MICHON R J Primary
 Pulmonary Hypertension *Am J Med* 11 686 1951
 DUNN C K Pulmonary Edema and Inflammation
 Cambridge Mass Harvard Univ Press 1945
 EBERSON F C, KROHL R F, and DERRICK J E Vari-
 eties of the Bronchial Veins as a Source of Hemoptysis in
 Mitral Stenosis *Am Heart J* 77 445 1944
 GORDON C A, and DAI T J Conditions Which Result in
 Increased Pressure Within the Lesser Circulation *Am J*
Roentgenol 61 76 1949
 GRANTER R G and HEARN J B Intrapulmonary Septal
 Lymphatic Lines (B Lines of Kerley) *J Fac Radiol*
Brit 7 64 1955
 HARRISON W and LEBROW A A The Effects of Massive
 Interstitial Infiltrations with Special Reference to Pulmo-
 nary Congestion and Edema *Lancet* *i* Biol & Med 76 1
 1954
 HILFELDER G, and HINSON K F W An Anatomical
 Explanation of the Formation of Butterfly Shadows
Thorax, 9 199 1954
 HINCH, I S Pulmonary Changes in Pheochromocytoma
Radiology 26 449 1956
 JONES P J, and GRIFFITH J Q Chest Roentgenograms in
 Pulmonary Arteriovenous Malformations Secondary to Pul-
 monary Arteriovenous Malformations *Am J Roentgenol* 46 57 1941
 KROHL R F The Etiology of Pulmonary Arteriovenous
 Malformations (Syndrome) *Am J Med Sc* 719 157 1950
 LEVINE B On the Recognition and Significance of Pleural
 Effusions *Am Heart J* 49 571 1955
 LEE P, PALAN P Y, LINDEN J, and CARROLL J The
 Initial Changes in Cardiac Disease *J Intern Med* 1
Chir Thoracique 3 141 1949
 SIMMONS S C, and KIRLEY P A Text Book of X Ray
 Diagnosis by British Authors 1951 1113 404 405
 SHORT D S Radiology of the Lung in Mitral Stenosis
Brit Heart J 17 33 1955
 SPAIN D M Mechanisms Involved in the Production of
 Pulmonary Hypertension *New York State J Med Sc*
 1901 1951
 THOMPSON A C, and STEWART W C Hemoptysis in
 Mitral Stenosis *JAMA* 144 21 1951
 WELLS S Pulmonary Congestion and Edema *Bull New*
York Acad Med 18 93 1942

DOUGLAS I Uremic Leds
renal, 58 620 1947
 GOODWIN W A Pulmonary Edema *Am J Roent*
Radiology, 51 58
 GOODWIN J F, STINER R F, and LOWE K G The Pul-
 monary Arteries in Mitral Stenosis Demonstrated by
 Angiocardiography *J Fac Radiology* 4 21 1952
 GORDON C A, and TORRANCE D J Pulmonary Edema
Am J Roentgenol 73 366 1955
 HAYWARD G W Pulmonary Oedema *Brit Heart J* 11 1161
 HOPPER H C and WISLER R W Uremic Pneumonitis
Am J Path 31 261 1955
 JACKSON F The Radiology of Acute Pulmonary Edema
Brit Heart J, 13 103 1949
 OLSON O Some Radiological Problems Connected with
 Bright's Disease *Brit J Radiol* 27 86 1954
 PUGHARD M I, DAVIS P M, and ARNOLD G M Peri-
 pheral Echinemia of the Lung *Brit J Radiol* 27 93 1954
 REYNOLDS R A, LEVY A H, and COLE A M Pulmonary
 Manifestations of Azotemia *Am Roentgenol* 46 802
 1941
 REYNOLDS S On the Roentgenologic Picture of Pulmonary
 Edema *Acta radiol* 10 169 1949
 ROUSSEAU C Le poumon azotémique Etude radiologique
J Med Lyon 19 467 1938
 SEXTON R and WATTS J P Roentgenological and
 Pathological Observations in Antigenic Pneumonitis Its
 Relationship to the Collagen Diseases *Am J Roentgenol*
 66 57 1951
 TRACY J, BARCLAY A E, FRANKLIN K J, DANIEL P M
 and PARRISH M L Studies of the Renal Circula-
 tion in the Renal Circulation
 Springfield Ill Charles C Thomas, Publisher 1948

HYDROTHORAX

DOUGLAS W The Clinical Significance of Some Peculiarities
 of the Circulation in the Kidneys Liver Lungs and
 Heart *New England J Med* 236 773 1947
 HILTON J A, JERGENS J J, BARNETT V J, and PARRISH
 T W Localized Interlobar Pleural Effusion Due to
 Congestive Heart Failure *Arch Int Med* 96 180 1955
 MEEK F M and LAMME S The Preponderance of
 Right Hydrothorax in Congestive Heart Failure *Ann*
Int Med 25 916 1946
 ROBERTSON R F Interlobar Hydrothorax in Cardiac Fail-
 ure *Brit Heart J* 13 117 1951
 STEIN I D and SCHWARTZ J B Interlobar Effusions in
 Patients with Heart Disease *Am Heart J* 10 210 1944
 WELLS W, BOYCE K R, and GERTEN W J Localized
 Interlobar Effusion in Congestive Heart Failure *Ann Int*
Med 38 1177 1953
 WILSON P D, ALGER S, and VINCIGUERRA C R Hydrothorax
 in Congestive Heart Failure *Am J Med Sc* 214 243
 1947

AZOTEMIA WITH PULMONARY MANIFESTATIONS

BUTTS H E and SIMMONS S C Pulmonary Changes in Uremia
JAMA, 144 819 1950

Figure 66 Pulmonary infarction A (Upper left) Irregular densities in left lower lobe, obscuration of left costophrenic sinus increased bronchovascular markings and linear horizontal striations in right lower lobe B (Upper right) Left lateral projection shows a roughly triangular density occupying the basal portion of the left lower lobe, encapsulated fluid above diaphragm prominence of interlobar fissure (Sudden onset of chest pain fever signs of consolidation and pleural friction rub over left base) C and D (Lower left and right) Six weeks later complete resolution of basal densities except for blunted costophrenic sinuses

CAVERNOUS HEMANGIOMA OF THE LUNG

- BAER, S., BEHREND, A., and GOLDBERG, A. L. Arteriovenous Fistulas of the Lung. *Circulation*, 1602, 1950
- BAKER, C., and TROUNCE, J. R. Arteriovenous Aneurysm of the Lung. *Brit Heart J*, 11 109, 1949
- BEIERMANN, W. H., and BARON, F. X. Pulmonary Arteriovenous Aneurysm with Secondary Polycythemia. *J.A.M.A.*, 134 1069, 1947
- BISGARD, J. P. Pulmonary Cavernous Hemangioma with Arteriovenous Fistula, Surgical Management. Case Report. *Ann Surg*, 126 965, 1947
- BLADES, B., and BEATTIE, C. Pulmonary Arteriovenous Aneurysm. *J Mt Sinai Hosp*, 18 195, 1951
- BOYERS, W. F. Rupture of Visceral Hemangioma as a Cause of Death. With Report of a Case of Pulmonary Hemangioma. *Nebraska M J*, 21 55, 1936
- BRUNY, A. J. Telangiectasis of the Lungs with Two Case Reports of Hereditary Hemorrhagic Telangiectasia with Cyanosis. *Quart J Med*, 19 219, 1950
- ERR, L. A., FOLDES, J., PROCTOR, F. V., and WAGNER, F. B., JR. Pulmonary Hemangioma with Pulmonary Artery Aortic Septal Defect. *Am Heart J*, 38 766, 1949
- ETTINGER, A., MAGENDANTZ, H., and RUSSO, E. A. Arteriovenous Aneurysm of the Lung. *Radiology*, 53 261, 1949
- FORSEY, J. H., MANOV, H. W., and JAMES, L. A. Cavernous Hemangioma of the Lung. *Ann Surg*, 131 418, 1950
- GOLDMAN, A. Cavernous Hemangioma of the Lung, Secondary Polycythemia. *Dis Chest*, 9 479, 1943
- GOLDMAN, A. Pulmonary Arteriovenous Fistula with Secondary Polycythemia Occurring in Two Brothers, Cure by Pneumonectomy. *J Lab & Clin Med*, 32 330, 1947
- HEPBLUM, J. and DAUPHINEE, J. A Successful Removal of Hemangioma of the Lung Followed by Disappearance of Polycythemia. *Am J Med Sci*, 204 681, 1942
- HEYDE, E. C. Hereditary Hemorrhagic Telangiectasia. A Report of Pulmonary Arteriovenous Fistulae in Mother and Son. Medical (Hormonal) and Surgical Therapy of this Disease. *Ann Int Med*, 41 1042, 1954
- LINDSAG, G. E., LIEBOW, A., KALSEL, H., and JANZEN, A. Pulmonary Arteriovenous Aneurysm. *Ann Surg*, 132 591, 1950
- MAIER, H. C., HINEMELSTEIN, A., RILEY, R. L., and BLUM, J. J. Arteriovenous Fistula of the Lung. *J Thoracic Surg*, 17 13, 1948
- MAKLER, P. T., and ZION, B. Multiple Pulmonary Hemangioma. *Am J Med Sci*, 211 261, 1946
- MOYER, J. H., and ACKERMAN, A. J. Hereditary Hemorrhagic Telangiectasia Associated with Pulmonary Arteriovenous Fistula in Two Members of a Family. *Ann Int Med*, 29 775, 1948
- READING, H. A Case of Congenital Telangiectasis of the Lung Complicated by Brain Abscess. *Texas J Med*, 28 462, 1932
- ROOFS, C. B. Cavernous Hemangioma of the Lung with Secondary Polycythemia. *J.A.M.A.*, 110 1914, 1938
- SEAMAN, W. B., and GOLDMAN, A. Roentgen Aspects of Pulmonary Arteriovenous Fistula. *Arch Int Med*, 89 775, 1948

- SMITH, H. L., and HORTON, H. T. Arteriovenous Fistula of the Lung Associated with Polycythemia Vera. Report of a Case in Which the Diagnosis was Made Clinically. *Am Heart J*, 18 589, 1939
- STEINBERG, I., and MCCLENNAN, J. Pulmonary Arteriovenous Fistula. *Am J Med*, 19 549, 1955
- TALBOT, T. J., and SILVERMAN, J. J. Asymptomatic Arteriovenous Fistula of the Lung. *Arch Int Med*, 90 569, 1952
- WATSON, W. L. Pulmonary Arteriovenous Aneurysm. *Surgery*, 22 919, 1947
- WEISS, E., and GASLI, H. M. Pulmonary Arteriovenous Fistula and Telangiectasia. *Ann Int Med*, 41 989, 1954
- WHITE, P. D. *Heart Disease*. New York, Macmillan Company, 1944
- YATER, W. M., and GIFFIN, H. M. Pulmonary Arteriovenous Fistula (Varix). Review of the Literature and Report of Two Cases. *J.A.M.A.*, 141 581, 1949

PULMONARY EMBOLISM AND INFARCTION

- BARBER, N. W., NYGAARD, K. K., WALTERS, W., and PRIESTLEY, J. T. A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. *Proc Staff Meet, Mayo Clin*, 15 769, 1940
- BERLIN, D. S., FINE, J. P., and LESLIE, L. W. Correlation of Postmortem Pathological Observations with Chest Roentgenograms. *Radiology*, 57 361, 1951
- ELLIS, F. H., JR., GRINDLAG, J. H., and EDWARDS, J. E. The Bronchial Arteries II. Their Role in Pulmonary Embolism and Infarction. *Surgery*, 31 167, 1952
- FOWLER, E. F., and BOLLINGER, J. A. Pulmonary Embolism. A Clinical Study of Ninety Seven Fatal Cases. *Surgery*, 36 650, 1954
- HENDERSON, E. F. Fatal Pulmonary Embolism. A Statistical Review. *Arch Surg*, 15 231, 1927
- JARRELL, S. R., and OLSSON, S. E. Roentgenological Studies of Experimental Pulmonary Embolism Without Infarction. *Am J Roentgenol*, 60 460, 1948
- SHAPIRO, R., and RIGLER, L. G. Pulmonary Embolism Without Infarction. *Am J Roentgenol*, 60 460, 1948
- SOLCHERAY, P. H., and OLOCHIN, B. J. Cavitation Within Bland Pulmonary Infarcts. *Dis Chest*, 24 180, 1953
- TOWERS, A. Pulmonary Embolism. Incidence and Significance. *J.A.M.A.*, 156 209, 1954
- WESTERMARK, N. *Roentgen Studies of the Lungs and Heart*. Minneapolis: University of Minnesota Press, 1948
- WRIGHT, I. S., and FOLEY, W. T. Pulmonary Thromboembolism. Diagnosis and Treatment. *New York State J Med*, 52 1994, 1952

Diagnosis: The Changing Scene

Introduction

The diagnosis and treatment of pulmonary diseases and this applies to other diseases as well changes with the times. In addition to matters of immediate concern to the patient to be discussed shortly, the well informed physician has to be aware of certain environmental factors which may also have a bearing on the problem although indirectly. The physician needs to keep abreast of changing fashions of medicine the implications of an aging population of the changing incidence and pathologic picture of certain diseases also the current status of new made diseases. Even advances on the socioeconomic front including the increasing use of chest x rays, the rapid development of disease detection clinics and the increasing facilities available for hospitalization of the sick or supposed sick carry with them certain repercussions relating to the diagnosis and treatment of disease.

CHANGING FASHIONS IN MEDICINE

Sosman makes some pertinent comments to the effect that a physician's approach to a problem is largely conditioned by what he has been taught and the mode of thought in his immediate environment. Currently the laboratories and scientific instruments are playing the major role. The concept of gross pathology as the basic disturbance underlying diverse processes and the production of symptoms has been relegated to the background. This is the metabolic biochemical electrolyte era. As a forceful illustration of this new approach to medicine I recently heard a young physician state in all seriousness that a patient under his care had died in electrolyte balance. It brings to mind the macabre jest of

last year when a patient with acute pneumonia under oxygen was said to have died with pink cheeks.

It is true that most of the conditions described in these pages require laboratory tests in establishing a diagnosis and in following the course of treatment often elaborate procedures available only in well equipped institutions. But the first step in approaching a problem is looking at and talking to the patient and seeing the latter as a distressed person in an unhappy environment rather than as a biochemical phenomenon. This faculty is acquired by the physician in the clinic and at the bedside not at the laboratory. The current surge in importance of physiology as a major discipline of medical education promises to serve as an instrument of teaching the physician the importance of dealing with the patient as a person regardless of the nature of the disease of which he may or may not suffer.

IMPLICATIONS OF AN AGING POPULATION

Since 1900 the number of persons over sixty five years of age in the United States has quadrupled those in the age group from forty five to sixty four has tripled. It is estimated that within a decade or two the average span of life for the population of the United States may reach seventy years approximately one third composed of people over forty five years of age. Insofar as it pertains to intrathoracic diseases one may expect that, as the population structure shifts to the elderly, physicians will encounter an increasing number of patients with degenerative lung diseases including fibrosis and

emphysema granulomatous lesions neoplasms as well as pulmonary manifestations of cardiovascular and systemic disturbances

In addition to the changes in the lungs the aging chest is accompanied by physiologic alterations in the thoracic cage itself which may be mistaken for pathologic processes within the lung parenchyma. Evans has drawn attention to some of the modifications that occur in thoracic structures in the process of aging. A small shrunk breast in an aged female may simulate malignant metastatic disease. Pronounced arthritic changes in a circumscribed portion of the spine may appear as an abnormal mediastinal density. A tortuous aorta may be mistaken for a pulmonary neoplasm. This applies also to a buckled prominent artery due to elongation or dilatation of the vessel. An enlarged pulmonary artery especially on the right side may cause an undue prominence of the root shadow.

IMPLICATIONS OF THE CHANGING CHARACTER OF DISEASES

Preventive measures and antimicrobial treatment have brought about a dramatic decline in the incidence of the acute pneumonias. The reduced incidence of this disease is reflected not only in daily practice but also at autopsy. Can non almost bemoan the fact that our residents and medical students now learn about the pathologic aspects of lobar pneumonia only from books from the reminiscences of older clinicians and pathologists and from museum specimens. As a result of the reduced incidence of the acute pneumonias there is a diminishing number of postpneumonic empyema and bronchiectasis. The decline of tuberculosis has relegated this one time scourge of mankind to a secondary place among major killers. How long will it be before the captain of the men of death follows the fate of pneumonia only time will tell. At present an elderly person who presents himself with cough or a change in the quality of the cough or an atypical pneumonia or blood spitting is more likely to bring to mind the possibility of the underlying cause being a pulmonary malignancy rather than tuberculosis.

IMPLICATIONS OF CHANGING FORMS OF TREATMENT

Present day knowledge is not sufficiently advanced to assess the role which the widespread use of chemotherapy and antibiotics are playing in changing the pathologic pattern of infections. Cannon quoted previously points out that one time lethal diseases such as lobar pneumonia purulent meningitis, mastoiditis, puerperal sepsis, septicemia and venereal diseases have either been rendered innocuous or practically abolished. These diseases have gradually vanished from the necropsy room so that life in the morgue has become correspondingly placid. The once common terminal pneumonia the friend of the aged is now so seldom seen that at times one wonders about the mounting therapeutic obstacles to the very act of death itself.

As serious microbial infections are being encountered less often there is an ever increasing number of resistant strains of bacteria developing as a result of antimicrobial therapy. Current interest centers on the development of superimposed infections due to antibiotic suppression of drug sensitive microorganisms. One is confronted with increasing numbers of pulmonary infections caused by fungi especially *monilia*, staphylococci and of *pseudomonas* and proteus types resistant to antibiotics. Of late discerning surgeons are becoming less dependent on antibiotic umbrellas and more on meticulous surgical technique. Penicillin and other potent antibiotics are being reserved for rainstorms rather than for summer showers (Bitten).

The emergence of drug resistant acid fast bacilli as a result of prolonged use of streptomycin, paraaminosalicylic acid and isoniazid in the treatment of tuberculosis is a problem the ramifications of which are still to be determined. Recent communications from several centers where large numbers of tuberculosis patients are on ambulatory treatment are revealing an increasing incidence of tuberculosis in infants as a result of contact infection at home. Of particular significance is the fact that cultures obtained from the gastric contents and spinal fluids of these infants are showing a decided increase

in strains of tubercle bacilli which are resistant to antituberculosis drugs

The widespread use of potent antimicrobial agents may also be a factor in the rising incidence of diffuse interstitial pulmonary fibrosis of undetermined etiology. As indicated in Chapter 6 it is suspected that the increasing incidence of diffuse interstitial fibrosis may be due in part to premature organization of pulmonary exudates as a result of the widespread and often indiscriminate use of potent antimicrobial agents. There appears to be also an increase in the incidence of disseminated lupus erythematosus, scleroderma, dermatomyositis, polyarteritis nodosa, rheumatoid states and other disturbances of the collagen group of diseases. To a major extent this increase is only apparent because of timelier recognition of these diseases and the nostic help furnished by newer tests. But in the increase may be due to the allergic reactions which often accompany sulfonamide and antibiotic treatment. Bird has drawn attention to the fact that the history of new drugs indicates that not all their potential dangers are immediately apparent also that recently drugs have been introduced for specific purposes that may actually produce complete syndromes.

Studies on the late reactions to hypotensive drugs indicate that a new man made disease is on the horizon. Dustan and co workers reported on a group of patients under prolonged hydralazine (Apresoline) treatment who presented an unusual rheumatic and febrile syndrome characterized in its milder phase by rheumatoid arthritis and in its severer form by symptoms of acute systemic lupus erythematosus including the occasional finding of L.E. cells. Of particular sig-

nificance from the viewpoint of the present discussion is the occasional occurrence of unexplained pneumonitis as well as pleural and pericardial effusions which can be controlled with ACTH and cortisone. The hydralazine syndrome which simulates a collagen disease occurs in about 10 per cent of patients treated with the drug.

Morrow and co workers reported on the effects of a combination of 1 hydrazinophthalazine and hexamethonium chloride (Hyphen) used in the treatment of 250 patients with hypertension. Among the side effects these investigators also found a number of patients with transient arthralgia indistinguishable at first from acute rheumatoid arthritis and after prolonged treatment from disseminated lupus erythematosus. Among the patients who died there were eight deaths due to apparent pulmonary complications. The findings in five were those of an interstitial pneumonitis rapidly progressing to death without the development of chronic cor pulmonale. The picture was in keeping with that described by Hamman and Rich. Morrow and co workers comment on the fact that since they were able to add a significant number of cases to the fourteen previously collected from the literature by Kahn, Peeler and myself it would indicate that the interstitial pneumonitis probably introduced by the therapy is a new disease chemically produced.

Bird introduces his timely discussion on the hazards of modern diagnosis and therapy with the quotation: First of all be sure you do no harm. *Primum non nocere*. In other words if in doubt of the diagnosis it is safer to withhold potentially dangerous agents.

CLINICAL HISTORY

Next in importance to the chest x-ray in the diagnosis of pulmonary disease is the clinical history. In his haste for objective findings the busy physician sometimes fails to listen to the patient's complaints. But the more experienced the physician the more time he takes in asking

Diagnosis

questions and less in thumping the chest. He has learned that a provisional diagnosis can often be made on the basis of the history alone. As Bird aptly remarks: Of all the technical aids which increase the doctor's power of observation none comes even close in value to the skillful use of words of the patient.

I recently had under observation a woman of fifty who showed in the chest x ray irregular but somewhat circumscribed densities in the right lower lobe, also infiltrations in the lingula (Figure 67A). Sarcoidosis, neoplasm and inflammatory disease were suspected but a diagnosis could not be established in spite of thorough studies including bronchoscopy and scalene node biopsy. At one interview, the patient offered the information which I should have obtained by direct questioning that for a period of fifteen years she had been taking at bedtime a mouthful of mineral oil directly from a gallon bottle, it was cheaper by the gallon. It was not difficult to ascertain the fact that on many occasions she gagged, especially when the bottle was full and top heavy. Obviously, in the course of years variable amounts of mineral oil had been aspirated into the lower air passages and caused a chronic pneumonitis. A chest x ray taken several years previously became available and it showed similar infiltrations.

Oil aspiration or lipid pneumonia is a frequent occurrence in debilitated persons who because of the presence of cardiospasm neurologic or cancerous disturbances are unable to swallow properly, thereby allowing oil medication to enter the larynx and lungs. Even healthy individuals may develop lipid aspiration pneumonia as a result of energetic self medication with oily nose drops or laxative oils.

Good history taking requires skill, tact and knowledge on the part of the physician. Skill in asking leading questions without seeming to stress their importance, tact in allowing the patient to "blow off steam" and knowledge in evaluating the significance of various complaints. 'Successful talking with patients contrary to common opinion, is more a science than an art and a good bedside manner is a myth unless it has its roots in scientific understanding.' (Bird)

In most instances an adequate history can be obtained in a short time, occasionally considerable time is necessary. A fortuitous remark may throw an entirely different light on a seemingly perplexing problem. Taking a history cannot be relegated to a secretary. How the patient answers is as important as what is said. In obtaining

a history it is well to bear in mind that placid individuals are apt to minimize their complaints high strung individuals magnify them. Constant interruptions on the part of the examiner and undue harping on a few symptoms may cause the patient to give misleading information for fear that his intelligence is being questioned. After repeated questioning any audible sound in the chest may become a wheeze, a sensation of cold, a chill, a slight chest discomfort, an excruciating pain, streaked sputum, a mouthful of blood.

If the onset of the disease is recent and relatively acute, and events are fresh in the patient's mind, the history elicited is usually reliable and the physician has little difficulty in reconstructing a complete sequence of events. If the illness is of long duration and of low-grade intensity, the physician may have to do considerable probing. If there is a family history of tuberculosis it may be difficult to elicit this fact, especially if the patient is being interviewed in another's presence. The mere fact that a person had been exposed to tuberculosis does not necessarily indicate that tuberculosis is the cause of the complaints. More often it is not. Adequate histories are also difficult to obtain in patients with pulmonary infections following alcoholic intoxication.

Difficulties in obtaining reliable histories are particularly great in the case of patients who have had treatment for psychiatric conditions. In one patient, under my care, the presence of considerable pain in the left upper chest and a circumscribed density in the upper aperture of the thorax seemed in keeping with a malignant neoplasm (Figure 67B). A thorough study, including bronchoscopy, was unrevealing. After considerable probing, the husband offered the information that he had noted the wife's breath had been offensive at times. A history of foul odor to the sputum had been sought for but had not been obtained previously probably because the patient had been receiving penicillin and was not expectorating. Additional questioning soon established the fact that the patient had recently received shock treatment for a depressive state. The chest x ray taken prior to the shock treatment was then obtained and it showed no abnormalities. Obviously one was denying

with an aspiration lung abscess. After several months intensive penicillin treatment the lesion resolved completely.

The fact that the symptoms may be of recent onset does not necessarily imply recently acquired disease. The present illness may be due to an exacerbation of a long smoldering focus. This applies especially to tuberculosis. Furthermore the mere fact that an individual has had the disease for a comparatively long time does not rule out the possibility that one is dealing with a malignant neoplasm. Bronchiogenic carcinoma may evolve over a period of several years and not come to light until late in its evolution. Finally the fact that a patient has acute symptoms referable to the chest does not necessarily indicate that the disease found in the chest is the cause of the symptoms. An acute respiratory infection often prompts the physician to take a chest x ray and a silent neoplasm, tuberculosis or other con-

dition discovered in this manner. Children are often admitted to hospitals with acute respiratory symptoms. The obtaining of a positive tuberculin test and evidence of a primary tuberculous infection in a lung in the chest x ray is often a matter of concern. Almost invariably the acute respiratory symptoms turn out to have had nothing to do with the finding of the tuberculous infection, usually inactive or undergoing arrest.

Of interest in the past personal history of a patient is information relative to the country of birth, in the case of immigrants or sojourns in distant parts of the world, in the case of native born. It is also important to inquire of the patient's recent travels in the United States as well as in foreign countries where certain diseases are endemic and which may affect the lungs. Parasitic infections acquired in the course of travel often present difficulties in diagnosis. Immigrants from the Mediterranean basin may harbor



Figure 67
Bilateral pneumonia due to aspiration, failed to respond to treatment.

pneumonia
lower
of

Irregular densities and reticular pattern in the lower lung fields (Lipid aspiration pneumonia). Dense circumscribed infiltration in the chest. Sputum examinations negative. History obtained of shock. Resolution of density after



Figure 68 Pulmonary coccidioidomycosis A (Left) Thin walled cavity in left upper lobe moderate degree of surrounding infiltration linear density at base of right upper lobe (Resident of Arizona history of cough and bloody expectoration tuberculin skin test negative coccidioidin test positive coccidioides immitis organisms present in sputum) Pulmonary histoplasmosis B (Right) Miliary calcifications evenly distributed throughout both lungs (Initial chest x ray at age of fourteen years revealed scattered soft infiltrations at the age of twenty two infiltrations underwent calcification as noted Tuberculin skin test negative histoplasmin positive) (Courtesy Dr H G Zwerling Berkeley Cal)

echinococcal disease which may simulate pulmonary tumor Brucellosis is found in certain parts of the United States as well as in Europe and South America Various parasitic infections were acquired by the Armed Forces in the Far East during World War II In the United States coccidioidomycosis is concentrated chiefly in California and Arizona (Figure 68A) histoplasmosis in the Eastern Central and Midwestern states (Figure 68B) Both may give rise to pulmonary disease Space does not permit of a more extended review of the subject

It is also essential that information be obtained of operations recently performed under general anesthesia or recent tooth extractions and tonsillectomy Berson and Adriani have shown that silent regurgitation and aspiration of gastric contents leading to pulmonary infection may occur even during smooth endotracheal anesthesia the anesthetist being unaware that such had taken place In difficult inductions the incidence of regurgitation and aspiration is considerably greater than that occurring during smooth inductions

Although diseases of infancy and childhood may attack adults and vice versa there is a defi-

nite age and seasonal incidence of certain respiratory infections the knowledge of which is important in diagnosis The common cold in influenza and pneumonia are infrequent during the warm months, the number of cases begins to increase thereafter reaching a peak in January Influenza is a disease of cold weather The Spring months favor infection with the coccus group of bacteria Congenital malformations are occasionally the cause of acute respiratory distress in the newborn Developmental defects may remain latent and manifest themselves in later years as a result of repeated lung infections Such defects may occur in several members of the family The association of transposition of the viscera with sinusitis and bronchiectasis so called Kartagener's syndrome is being reported with some frequency Areal described four instances in one family of total visceral inversion with congenital bronchiectasis and cystic lung The occurrence of familial hemorrhagic telangiectasia associated with pulmonary arteriovenous fistulae has been discussed in Chapter 11 Bronchopneumonia in children may complicate acute contagious diseases notably measles and whooping cough Bronchiectasis in later life may occur

sionally be traced to such episodes. On the whole, the school age is fairly immune to serious lung disease.

The adolescent girl and young woman is susceptible to tuberculosis although the disease is now being discovered with greater frequency in older age groups. Adulthood is the age in which pneumonia is most prevalent. A failing heart is a frequent cause of symptoms referable to the chest, the first evidence of cardiac decompensation often being a hacking cough and basal rales. Chronic bronchitis and nonspecific bronchopulmonary infections are more frequent with advancing age. Many elderly individuals with chronic pulmonary fibrosis and bronchiectasis developed their diseases during the pandemic of 1917-1918. Some trace their "lung trouble" to inhalation of noxious gases during World War I. Bronchiogenic carcinoma, as mentioned is now the most frequent serious lung disease of middle and advancing age, particularly in the male. Upper lobe fibroid tuberculosis associated with emphysema often masquerades as chronic bronchitis. The fact that a patient has, or is known to have had, pulmonary tuberculosis does not exclude the presence of a malignant pulmonary neoplasm. The occurrence of the latter in patients who had been treated many years previously for tuberculosis is not at all rare (Figure 69).

With respect to occupational lung diseases, it should be noted that silicious dusts may continue to exert their deleterious effects long after the individual has broken contact with the irritant (Figures 70A and B). Organic dusts such as fur, feathers, cotton and wool, although they may not cause demonstrable disease in the chest x-ray, are often the cause of chronic cough. In view of the increasing incidence of carcinoma of the lung, it might be well to point out that certain occupations predispose to the development of malignant pulmonary neoplasms. The carcinogenic effects of smoking on the lungs is well documented. In puzzling cases, the information that the patient had been a heavy smoker for many years is often sufficiently impressive to swing the balance in favor of the condition being carcinoma rather than some other cause. In sus-

pected carcinoma in the female, the fact that the patient had been a nonsmoker carries considerable weight in excluding carcinoma because of lower incidence of the disease in the female sex in general. Among occupational hazards, it should be noted that workers exposed to inhalations of chromate dust or pigment, asbestos dust and radioactive substances have a higher incidence of carcinoma of the lung than do workers in other occupations.

Before concluding this section, a few remarks on the psychosomatic aspects of pulmonary disorders are in order. One encounters patients, usually women, who complain of "inability to catch the breath" or "a feeling of weight in the chest" or "a lump in the throat" and similar expressions for which no adequate cause can be found. Tachypnea, as a form of respiratory neurosis, may end in tetany as a result of hyperventilation. A rather frequent occurrence is a loud unproductive cough encountered in patients who may have been told, long proved unfounded, that they harbored some lung disease. The constant cough, in itself becomes a source of irritation and a vicious cycle is established. One gets the impression that in some of these individuals the cough is a defense reflex which has outlasted the original condition, if there ever was a physical basis. It should be emphasized, however, that before one makes a diagnosis of a neuropathic constitution, a chest x-ray should be taken and the upper air passages carefully examined.

THE PHYSICAL-X-RAY EXAMINATION

It is a daily experience to discover in a chest x-ray evidence of more disease in the lungs than is realized from the patient's symptoms and physical findings. But after one has viewed the film, additional data are often obtainable on questioning the patient and reexamining the chest. The appearance of the chest x-ray may prompt the physician to inquire about the individual's occupation, past illnesses, travels and to obtain further information which he might otherwise have neglected to do. A blunted costophrenic sinus or a thickened pleura may help in eliciting a history of influenza, pleurisy or pneumonia,

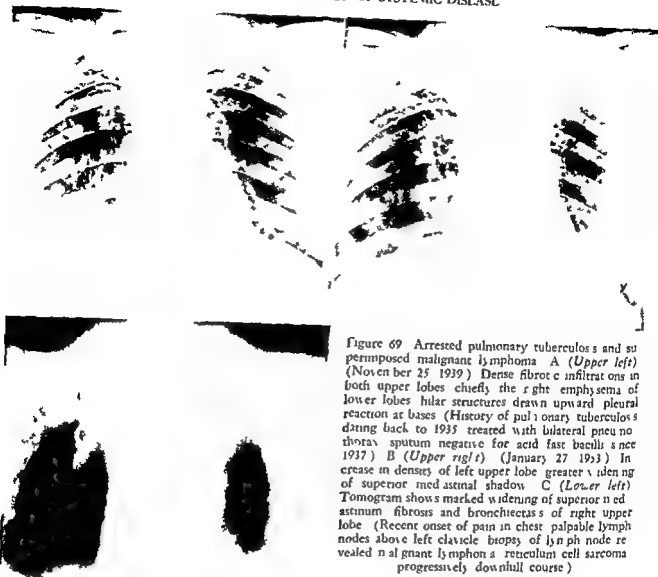


Figure 69 Arrested pulmonary tuberculosis and superimposed malignant lymphoma. A (Upper left) (November 25, 1939) Dense fibrotic infiltrations in both upper lobes chiefly the right emphysema of lower lobes hilar structures drawn upward pleural reaction at bases (History of pulmonary tuberculosis dating back to 1935 treated with bilateral pneumothorax sputum negative for acid fast bacilli since 1937) B (Upper right) (January 27, 1953) Increase in density of left upper lobe greater widening of superior mediastinal shadow. C (Lower left) Tomogram shows marked widening of superior mediastinum fibrosis and bronchiectasis of right upper lobe (Recent onset of pain in chest palpable lymph nodes above left clavicle biopsy of lymph node revealed malignant lymphoma reticulum cell sarcoma progressively downhill course)

long forgotten. An apical scar may prompt the physician to question about tuberculosis. Scattered calcified foci in both lungs may bring out the fact that the person had lived in parts of the country where histoplasmosis is endemic. The presence of diffuse pulmonary infiltrations may focus attention to the possible existence of a systemic disease. One may encounter an individual momentarily engaged in an innocuous occupation yet the film may disclose stigmata suggestive of silicosis or some other dusty occupation which the patient had forgotten to mention but easily recalled once the matter is brought to his attention.

Bearing the aforementioned in mind physicians who have occasion to examine large numbers of persons with suspected lung disease have been following in recent years a somewhat different routine than that generally taught in medical schools. After listening to the patient's complaints and examining the chest an x-ray is taken and studied. Following this preliminary orientation a more detailed history is obtained and a more critical examination made of the chest. If necessary, additional chest x-rays are taken in various projections to bring out specific details. This method of examining persons with suspected lung disease may not be adaptable to the daily

routine of the general practitioner, especially if there is no immediate access to roentgenographic equipment. But, in principle the need of integrating the chest x-ray within the scope of the physical examination is valid. In fact unless this is done the examination is incomplete. It is no criticism of the physician if he is unable to arrive at a precise diagnosis of a chest ailment when he attends a patient at home. The immediate consideration is the relief of distressing symptoms and secondarily the making of a correct diagnosis but the patient should be advised to have a chest x-ray taken as soon as he has recovered from the acute illness. If the disease shows no signs of relapse every effort should be made to have a chest x-ray taken at home by portable apparatus. Most textbooks on physical diagnosis have little to say on roentgenology in general much less on ways and means of dovetailing the latter with the physical examination. With an offhand suggestion that a chest x-ray be taken when in-

dicated, the best single means of diagnosing lung disease is relegated to the realm of laboratory procedures and the student is left with an erroneous impression of its real contribution. Such correlations as are made between physical signs and chest x-ray findings are more in keeping with postmortem pathology than with incipient disease. The reason for the relative neglect of the chest x-ray lies in the fact that the principles of physical diagnosis were firmly established long before the introduction of roentgenography and unfortunately, the former has retained its primary position.

By and large students of medicine are still being taught signs which have been shown to be incorrect or seldom demonstrable or of questionable value, at best. Few teachers of physical diagnosis dare admit that abnormal physical signs if elicited are better appreciated after one has seen the chest x-ray and reexamined the chest. Were this procedure taught to the student



Figure 70. Pneumoconiosis. A (Left) Hilar densities extending fanwise into adjacent zones linear and nodular infiltrations involving chiefly upper and middle portions of both lungs; hyperillumination of surrounding areas (Soft coal miner for twenty-two years). B (Right) Prominent hilar densities showing egg shell calcifications of lymph nodes throughout both lungs, emphysema of remainder of lung (Sulzberger tunnel). Siderosis (Soft coal miner for forty years).

the latter would then be in a position to understand why an area of impaired resonance may be caused by lung consolidation in one patient by a pleural effusion in another by consolidation plus fluid in a third or by some other abnormal state in a fourth. The suppressed breath sounds may then be revealed as due to emphysema, pneumonia, pleural effusion, consolidation or some other space occupying disease. The integration of the x-ray and the physical findings in the over all examination not only helps to account for the presence or absence of various abnormal conditions which may be encountered in the chest but it also serves to sharpen the physician's diagnostic acumen should a chest x-ray not be immediately available.

On the other side of the picture should be mentioned the fact that the chest x-ray does not disclose all pathologic states which may affect the lungs. Under such conditions the elicitation of abnormal physical signs in the presence of an apparently negative chest x-ray is in itself of diagnostic value. Inflammatory conditions of the tracheobronchial tree unless associated with pulmonary lesions are not demonstrable in the chest x-ray although they may be suspected from the history and physical signs. Likewise the physical signs may be more informative in the case of viral or chemical bronchiolitis or lesions of the cortical portions of the lungs.

Partial occlusion of a bronchus may give rise to a harsh rhonchus or wheeze over a limited area of the chest yet in the routine chest x-ray no significant alterations from the norm may be detected. The presence of bronchiectasis may occasionally be suspected from the routine chest x-ray alone especially if the history and physical signs are also suggestive. But in many instances the chest x-ray is within normal limits and in no case can an unequivocal diagnosis of bronchiectasis be made without a confirmatory bronchographic examination. Emphysema, one of the most frequent conditions encountered is easily missed in the chest x-ray. It is obvious therefore that although the chest x-ray broadens the

horizon and serves as a check on the physical findings it does not displace the latter.

One need not belabor the point that if there is one branch of medicine in which the student is in need of being brought up to date it is in the field of diagnosis of chest disease. The modern stethoscope is a more flexible tube than is the paper cylinder improvised by Laennec but to all intents and purposes the stethoscope is still largely a decorative piece rather than a precision tool and possibly a poorer conductor of sounds than the original makeshift. Let me hasten to add however that although the stethoscope is essentially the hallmark of the physician it is here to stay. Folded in the physician's hand or nestling around his neck or even peeling out of his coat pocket the mere sight of the instrument is often sufficient to drive pain away and start the patient on the road to recovery. Many a patient has been cured by the venerable family doctor who took time to listen to his woes and applied his ear to the covered chest. And not infrequently the old gentleman was somewhat hard of hearing.

The diagnosis of chest diseases evolves around the proper use of the chest x-ray. In conjunction with the history, physical signs and pertinent laboratory tests the chest x-ray completes a discipline upon which the physician has to depend for a reasonably accurate diagnosis. The pulmonary lesions occurring in the course of systemic diseases are usually deep seated and little concrete information may be obtainable not only from symptoms and physical signs but even from chest x-rays. Often the only recourse is the performance of an exploratory thoracotomy and the obtainment of a lung biopsy. But even the availability of the latter may shed little light since all too often the histologic features of the biopsy specimen are in keeping with one of several pathologic states. For these reasons the physician has to take into consideration not only what meets the eyes in the way of chest x-rays and biopsic material but in difficult situations he must also draw on a broad fund of knowledge of internal medicine.

Diagnosis: Symptoms and Signs

Introduction

COUGH, PAIN IN THE CHEST, DYSPNEA and other symptoms of ill health are individually of little help in differential diagnosis except for drawing attention to the fact that all is not well. But when combinations, a number of possibilities come to mind. For example, pain in the chest on respiration, associated with dyspnea, after a period of cough and bloodspitting suggests a pulmonary disease with secondary involvement of the pleura. On the other hand, pain in the chest, not related to respiration, associated with dyspnea, followed by cough and bloodspitting is more in keeping with myocardial infarction and pulmonary congestion. When a patient's complaints are analyzed in the light of the entire case history and chest x-ray findings, the symptoms assume major importance not only in diagnosis but also in prognosis.

Symptoms are caused in part by structural damage of the lungs and in part by functional disturbances with respiration and blood oxygenation. The former are expressed chiefly in cough, expectoration and chest pain, the latter, in varying degrees of anoxia, clinically expressed in dyspnea and cyanosis. In addition, there are symptoms of a more generalized nature such as fever, tachycardia, loss of weight and sweating. These need not be considered in detail here but it is well to point out that in the differential diagnosis of systemic diseases such symptoms and signs may be of greater significance than those referable to the chest.

Cough

Cough is among the first symptoms of lung disease to appear and among the last to disappear

The character of the cough may suggest the site of the disease. A persistent cough, without an accompanying wheeze, may be allergic in nature. Hypersensitive individuals are apt to cough for months after the mildest upper respiratory infections. A persistent postnasal discharge may be the focus. A latent middle ear infection or an hypertrophied uvula should not be overlooked in seeking a cause for unexplained cough, particularly if the latter is of a nonproductive, explosive variety. Patients with mitral stenosis associated with enlargement of the left auricle may cough as a result of elevation and compression of the left main bronchus. Cough is, of course a prominent symptom of decompensated heart disease associated with pulmonary congestion. A dry, spasmodic cough may be among the first symptoms of intraabdominal disease, painful if associated with subdiaphragmatic irritation. A suppressed, painful cough often accompanies regional invasion of lung by carcinoma.

As a rule, the louder and harsher the cough, the more likely is the seat of the disease in the trachea and larger bronchi. A "brassy" cough is occasionally heard if the trachea is compressed by a substernal thyroid, mediastinal neoplasm or an aortic aneurysm. The shorter, deeper and more painful the cough, the more apt is disease to be present in the parenchyma and pleura. Paroxysms of cough occur in bronchial asthma, whooping cough, bronchial obstruction and bronchiectasis. On rare occasion, a fit of coughing may produce unconsciousness with or without convulsions, so-called, laryngeal vertigo or, better termed, cough syncope. Unless the cause is obvious, a persistent cough, especially if asso-

ciated with unilateral wheeze calls for bronchoscopic examination. A pulmonary neoplasm, foreign body or other evidence of internal or external bronchial compression will often be found. Any unexplained cough in a patient of the cancer age deserves attention. If the chest x-ray shows the slightest abnormalities for which a cause is not readily ascertainable a bronchoscopy is in order.

EXPECTORATION

Usually but not invariably expectoration follows cough if the latter continues long enough. The cough tends to subside when it becomes productive. Women and children who swallow their sputum may eliminate the latter in the vomitus. I have encountered several patients with esophageal hiatus hernia in whom an emetic cough was a prominent symptom. The gross appearance, odor, color and quantity of sputum eliminated are to be considered in differential diagnosis but they are not dependable without additional findings. Catarrhal conditions of the trachea and bronchi give rise to thin mucoid sputum; deeper infections of the lung are associated with thick purulent secretion. Frothy, blood-tinged sputum is often encountered in pulmonary edema; viscid, dark brown sputum in pneumococcal pneumonia; slimy, sticky sputum in Friedlander pneumonia. Long continued expectoration of purulent sputum mixed with blood is a frequent occurrence in carcinomatous lung abscess. The foul odor of anaerobic pulmonary suppuration is a characteristic feature of the disease. It should be noted, however, that the foul odor may be suppressed by antibiotic treatment and that one may harbor a serious lung disease without much if any cough or expectoration.

In the presence of upper lobe cavitation there is little variation in the amount of sputum eliminated during the day because of the dependent drainage. Cavities situated in the lower lobes retain the secretions during the day when the patient is in the upright position. The sputum is eliminated in large amounts immediately on arising or on change of position when the contents of the cavity overflow into the main bronchi and

the cough reflex is excited. Many patients with chronic pulmonary suppuration learn to control their cough and expectoration and empty the bronchial contents at intervals.

HEMOPTYSIS

There is hardly a disease affecting the respiratory tract directly or indirectly which may not cause bloodspitting. The dilution and anastomoses of the pulmonary and bronchial blood vessels in the presence of disease, the intimate contact of the capillary bed with the alveoli and the external communication of the bronchi provide an ideal arrangement for bloodspitting. The remarkable thing is that the hemoptysis does not occur more often. Bloodstreaking may occur during acute lung infections when the affected parenchyma becomes engorged with blood. Copious amounts of blood are usually not expectorated due to early thrombosis and occlusion of the blood vessels. Except in instances of necrotizing pneumonias gross hemoptysis is uncommon. In acute lung abscess the initial symptom may be a profuse hemorrhage, the blood mixed with purulent matter.

Hemoptysis is encountered much more often in chronic bronchopulmonary than in acute diseases. Dilated bronchi or rigid cavities traversed by partially thrombosed blood vessels which have lost the support of the contractile elements of the lung are favorite sites of bleeding. Hemorrhage is therefore frequent in bronchiectasis, carcinoma, chronic lung abscess and fibroid tuberculosis. Occasionally the hemorrhage is fatal. As might be expected from the age incidence of these diseases, hemoptysis occurs more often in older age groups and more often in males. A notable exception is bronchial adenoma which is more common in young women. In the presence of caseous tuberculosis and other infectious processes associated with considerable discharge, hemoptysis is particularly dangerous because it predisposes to spread of the disease to uninvolved parts of the lungs.

It is often difficult to ascertain, even at autopsy, the site of the pulmonary bleeding. In bronchiectasis and malignancies affecting major bronchi

the bleeding usually originates in one of the bronchial arteries. Ulcerative diseases especially tuberculosis are more apt to involve branches of the pulmonary artery. The pulmonary veins are rather small until they reach the hilus and it is doubtful whether they give rise to significant bleeding. Bloodspitting occurs in the course of cardiac diseases associated with hypertension and arteriosclerosis of the lesser circulation. Mitral stenosis and congestive heart disease associated with pulmonary infarction are outstanding examples. Hemoptysis of cardiac origin is more apt to occur at night probably because of the increased pressure in the pulmonary circulation during sleeping hours. An infarcted lung may give rise to copious hemorrhages a point to be remembered since the condition may simulate carcinoma.

Blood dyscrasias and vitaminic deficiencies which cause alterations in either the constituents of the blood or the structure of the vessel walls are rare causes of bloodspitting. Obvious conditions causing hemorrhage such as foreign bodies and chest trauma need only be mentioned. So called hemoptysis of unknown origin is often due to tracheobronchial varices, dry bronchiectasis, new growths or nonspecific granulomatous tissue. The differential diagnosis may be established by bronchoscopic examination. It is noteworthy that shock or severe chest pain seldom accompanies hemoptysis of pulmonary origin alone. If shock occurs it is usually associated with a vascular crisis a condition most often encountered in infarction.

CHEST PAIN

Pain is a dramatic but not a significant diagnostic symptom of pulmonary disease. One of the salutary effects of pain in the chest is to cause the patient to seek medical attention. This explains partly the comparatively good prognosis of patients with pulmonary tuberculosis and several other diseases which begin with pleurisy. This also holds true to some extent for hemoptysis. Chest pain is often lacking in advanced lung disease and may be quite severe in the presence of limited involvement. An explanation

for this seeming paradox is found in the fact that the lungs and visceral reflections of the pleura possess no pain fibers. The parietal pleura on the other hand is exquisitely sensitive. According to Capps painful areas are concentrated chiefly over the lateral and ventral portions of the pleura and to a lesser degree over the dorsal aspect.

Irritation of the central or tendinous part of the diaphragmatic pleura often gives rise to referred pain in the neck, the site of origin of the phrenic nerve which has both motor and sensory fibers. Irritation of the costal portion of the diaphragm may give rise to pain not only in the lower thorax but also in the abdomen and lumbar regions corresponding to the distribution of the lower six intercostal nerves which supply branches to the periphery of the diaphragm. The exact mechanism in the production of pleural pain is not clear. Some believe that the pain is due to friction of inflamed pleural surfaces since relief occasionally follows an effusion. Some years ago when pneumothorax treatment of lobar pneumonia was in trial it was noted that separation of the pleural surfaces by air inflation in the cavity brought about marked relief in painful pneumonia. Others believe that the pain is caused by hyperalgesia and contraction of the intercostal muscles. Still others claim that the pain is due to tension or stretching of inflamed parietal pleura.

The sharp stielv pain aggravated on breathing which causes the patient to splint the affected side of the chest is a frequent occurrence in pleuritis of whatever origin. As a rule neither the severity nor the distribution of the pain gives an inkling of the nature or extent of the pleural or pulmonary involvement. Chest pain is encountered in spontaneously fractured ribs. Such stress fractures unassociated with demonstrable pulmonary disease or abnormality of ribs are not rare although they often remain undetected. The resulting area of callous formation in the affected rib may be mistaken for intrapulmonary disease. Intercostal neurilgia and herpes zoster are also frequent causes of pain. In herpes zoster the pain may precede the appearance of skin



Figure 71. Carcinoma of lung masquerading as bursitis. A (Left) Diffuse ill defined infiltration in left apex (Onset with pain in left shoulder treated with radiotherapy for suspected bursitis). B (Right) Six months later circumscribed homogeneous density in left upper lobe (Marked digital clubbing exploratory thoracotomy revealed a carcinoma firmly adherent to apex of chest wall and mediastinal structures nonresectable).

blisters for a number of weeks during which time a neoplasm may be suspected.

Pain in the upper chest may be caused by a carcinoma of the so called Pancoast type or by pressure of a cervical rib on the brachial plexus or by an hypertrophied scalenus muscle pressing on the plexus or by involvement of the phrenic nerve anywhere along its course. Rheumatoid arthritis or bursitis of the shoulder joint is a frequent cause of pain in the apical region. It might be mentioned that rheumatoid arthritis regardless where located may be an early manifestation of carcinoma of the lung (Figure 71). Rose and Edeiken described seven cases of nodular nontoxic goiter occurring in association with thoracic pain of a variable pattern. Evidence of coexistent myocardial disease was present in two cases. In six of the seven cases the goiter was partially or entirely intrathoracic. Following subtotal thyroidectomy the original thoracic pain either disappeared or was materially modified in all the patients.

Chest pain may be the result of cardiocirculatory disease (pericarditis coronary artery dis-

ease aneurysm and aortitis) as well as of abdominal disease (subdiaphragmatic abscess disease of the liver gallbladder or gastrointestinal tract). The character of the pain its location its relation to the respiratory cycle the presence of painful sensation along intercostal nerves and the presence or absence of fever must all be taken into consideration. As mentioned the time relationship between the appearance of chest pain and cough is occasionally revealing. If pain unassociated with other symptoms precedes the cough by an appreciable interval it suggests disease originating in the chest wall rib or intercostal tissues. If the pain follows cough it is more likely that the disease is primary in the lungs.

I have seen two instances of pain in the lower chest and upper abdomen in conjunction with so called periodic disease a condition to which Reimann has drawn particular attention. The pain comes in cycles increasing in severity to a point where the patient may require opiates and gradually subsides. During this period the patient may also have fever chills and be quite

all The pain in the lower chest is usually associated with pain in the upper abdomen and often arthralgias. The cause of this recurrent disorder which has a familial tendency is unknown. There are no specific means of treatment. Pain in the chest is also encountered in, so called, epidemic pleurodynia. The condition is usually associated with cough, slight expectoration and upper respiratory symptoms. The disease has certain features consistent with an acute viral infection since it occurs in epidemics but the exact cause is unknown.

DYSPNEA

Labored breathing due to anoxia depends on the severity of the oxygen lack on the momentary body requirements and the adequacy of the compensatory mechanism. Dyspnea is usually encountered in advanced stages of bronchopulmonary disease. It occurs early in disease only if there is a sudden reduction of lung volume as might follow a massive pleural effusion or a spontaneous pneumothorax or an obstruction of a major bronchus. In the last mentioned, the narrowing of the air passage has to be considerable before dyspnea results. Diseases affecting the terminal units of the lungs or the small divisions of the pulmonary artery, as encountered in miliary tuberculosis and pulmonary arteriosclerosis, are characterized by rapid, shallow respiration rather than labored breathing. Orthopnea is as a rule, not encountered in lung disease unless there is superimposed cardiac failure causing pulmonary congestion. A sudden occlusion of a major bronchus or a severe asthmatic seizure are among the few exceptions. Individuals with advanced tuberculosis, silicosis and emphysema may be dyspneic at the slightest exertion, yet be fairly comfortable when lying down. The appearance of orthopnea strongly points to cardiocirculatory failure. A practical etiologic classification of dyspnea is furnished by Burchell (Table 7).

Although cyanosis is usually associated with dyspnea, the latter may be present without cyanosis or be out of proportion to the former. Such discrepancies are of some diagnostic significance. Emphysematous states associated with an increase in corpuscular and hemoglobin content of the

TABLE 7

ETIOLOGIC CLASSIFICATION OF DYSPNEA

- I Mechanical impairment of ventilation
 - a Muscular weakness, as from poliomyelitis or myasthenia
 - b Skeletal fixation as from marked chest deformity or spondylitis
 - c Hydrothorax pneumothorax
 - d Ascites
 - e Tracheal obstruction bronchiolar obstruction and laryngeal factors
- 2 Impairment of pulmonary distensibility (elasticity)
 - a Pulmonary congestion
 - b Pulmonary fibrosis
 - 3 Pulmonary insufficiency (inadequate functioning alveolar tissue)
 - a Emphysema
 - b Extensive inflammatory disease of the pulmonary parenchyma
 - 4 Inadequate delivery of oxygen to tissues
 - a Arterial hypoxemia as from high altitude
 - b Anemia
 - c Cardiac failure
 - 5 Hyperventilation of central type as from acidosis
 - a Nephritic
 - b Diabetic
 - 6 Psychic

From Burchell *Proc Staff Meet, Mayo Clin* 27:49 1952

blood readily show cyanosis because of the presence of an abnormal concentration of reduced hemoglobin in the peripheral capillaries (at least 5 gr per 100 cc of blood or 7 per cent oxygen unsaturation). Conditions characterized by arteriosclerosis may reveal extreme degrees of cyanosis and comparatively little dyspnea. The most severe forms of cyanosis, unassociated with dyspnea, are encountered in congenital heart disease in which a septal defect causes a mixture of arterial and venous blood. Variable degrees of cyanosis are met in association with cavernous hemangiomas (see Chapter 11). If there is an insufficient amount of unsaturated hemoglobin in the blood, as might occur in anemia, the dyspnea may be quite severe without there being cyanosis. Likewise, diabetes and nephritis are often associated with hyperpnea or dyspnea without cyanosis. Lastly, there are conditions such as lymphangitic carcinoma of the lungs in which the mechanical interference with blood oxygenation would ordinarily be associated with cyanosis but in which the latter is neutralized by the marked anemia which may be present.

Physical Exploration of the Chest

The following remarks will deal with some practical aspects of the physical exploration of the chest. No attempt will be made to enter into details because in the diagnosis of systemic diseases with pulmonary manifestations, of the type described in these pages, the examination of the chest is characterized by the absence rather than the presence of distinguishing physical signs. By and large, in systemic diseases a careful examination of the patient as a whole is more fruitful than the examination of the chest. The appearance of the face and skin for stigmata of systemic disturbance, the palpation of the abdomen for enlargement of liver, spleen, other masses, or fluid, palpation for enlarged peripheral lymph nodes and similar examinations are important features in diagnosis.

INSPECTION

Observing the patient is a most important part of the physical examination. Too often it is the most neglected part. The medical student in his formative years cannot be taught inspection because it is based on experience. "To see is not enough; the accent lies on observation," a difficult art to cultivate (Wartenberg). The busy practitioner, in his haste to apply the stethoscope, neglects to develop this faculty. Yet, what a wealth of information is to be gleaned from simply observing the patient. At a glance one notes the approximate age and physique of the individual, whether the illness appears acute or chronic, painful or painless, whether it is associated with respiratory distress or not. One may be struck by the feverish, restless appearance of the patient with an acute pneumonia. The appearance of the emphysematous individual with barrel shaped chest and labored breathing leaves nothing to be desired in the way of a diagnostic aid. The sallow looking man past middle age with cigarette stains on the fingers and evidence of recent loss of weight, complaining of pain in the chest, brings to mind immediately a possible carcinoma. The foetid expectoration, digital clubbing and dyspnea are typical of chronic pulmonary suppuration. It is true that looking at the

patient will not reveal the early stages of lung disease but neither will the physical examination.

PALPATION

It is said of a famous clinician that he once made a diagnosis of tuberculous meningitis simply by putting his hand under the patient's bedcover and palpating an enlarged epididymis. Knowing the frequency with which tuberculous meningitis complicates urogenital tuberculosis, he immediately suspected a hematogenous disease and associated it with the patient's neurological condition. Many renowned physicians have similar anecdotes to their credit, usually of isolated, "snap shot," diagnoses, the many more mistaken diagnoses are charitably overlooked. In the hands of the average physician, palpation gives little information. This, of course, does not detract from the importance of palpating for enlarged lymph nodes, bulging or pulsating masses, displacements of the trachea or the position of the apex beat. Since the vast majority of pulmonary infarcts originate in the veins of the lower extremities, it is good practice to palpate the blood vessels in these locations. Benson and Zavala draw attention to the importance of palpating for areas of costochondral tenderness which may be a source of unexplained pain in the chest. The condition is believed to be the result of stress or trauma to rib structures which produce an irritation or sensitivity of one or more costochondral junctions. Originally described by Tietze, and often referred to as Tietze's syndrome, the condition is not infrequent.

PERCUSSION

Gross alterations in the physical state of the thorax and its contents may be detected by percussing symmetrical areas of each side. Airless lung tissue of significant amount, or fluid in the pleural cavity, decrease the normal resonance of the organ. Hyperresonance, even tympany, may be obtained if there is an increase in the air content of the thoracic cage as in the presence of emphysema, giant cavities or pneumothorax. Particularly informative is the percussion note over the lower borders of the lungs on inspira-

tion and expiration. An appreciable increase in the area of resonance as the diaphragm descends on inspiration betokens a well functioning lung and one probably free of gross disease. But as mentioned in the preceding chapter the percussion note is much more informative after one has examined the chest *in vivo*.

AUSCULTATION

With respect to changes in the character of the breath sounds it should be noted that normal breath sounds may be heard in the presence of diseased lung. Abnormal breath sounds in the normal auscultatory finding in pulmonary disease is either suppressed or exaggerated vesicular murmur. Contrary to a prevalent belief fluid in the pleural cavity easily transmits sounds unless there is obstruction of the main bronchi. In the presence of a moderate collection of fluid in the pleural cavity the resulting compression of the lung may cause suppression of the vesicular murmur but the tubular sound from the bronchi may be exaggerated.

Bernstein and White found that when the pressure of the pleural effusion is constantly positive through all phases of the respiratory cycle one may obtain bronchophony, tubular or amphoric breath sounds and even whispered pectoriloquy. The pressure must be sufficient to compress the parenchymal tissue down to bronchi of sufficient size to reduce these auscultatory findings. I have noted repeatedly that following pneumonectomy the breath sounds may be heard better on the side where the lung had been removed than on the side with the lung intact probably because the marked deviation of the trachea to the operative side transmits the breath sounds through the organized fibrous exudates and mediastinal structures which fill the hemithorax on the operative side.

Alterations in breath sounds are significant if accompanied by rales especially if the latter are confined to a limited area and persist after cough. If the rales disappear after cough for a variable interval they probably originate in bronchi and not in lung tissue. Deviation of the trachea distorts and displacement of a large bronchus of the patient's breathing the position of the chest and many other variables influence the character of the breath sounds. As a rule the larger the bronchus from which the rales originate the louder and harsher the sounds.

Disuse of large bronchi associated with loud rhonchi or wheezing rales may be audible without the aid of the stethoscope. In a detailed study of noises heard with the unaided ear at a distance from the chest Heim mentions the occurrence of this phenomenon in patients with pneumothorax, mediastinal emphysema, pneumopericardium, pulmonary air embolism, heart murmurs and several other conditions. According to Greene the bubbling, clicking and crunching sounds emanating from the chest in the presence of interstitial emphysema are due to the heart rubbing against emphysematous blebs. Other knocking sounds may be due to the sympathetic flexure of the colon in the presence of a left sided pneumothorax.

In conclusion it may be stated that the elicitation of abnormal physical signs in pulmonary diseases especially in conditions in which the lungs participate as part of a systemic disturbance is the exception rather than the rule. One may elicit abnormal physical signs which are in no way related to the basic disease. In fact they are more apt to be due to intercurrent infection, secondary cardiac diseases or other incidental causes.

Bibliography Chapters 12 and 13

BARR, D. P. Hazards of Modern Diagnostics and Therapy—The Price We Pay. *JAMA* 159:145, 1955.
BARTON, L. Use and Abuse of Ambroscs. *Foreign Letters, JAMA* 157:838, 1955.

BEAN, W. B. Precordal Noises Heard at a Distance from the Chest. *JAMA* 155:193, 1952.
BROOKS, I. H. and JAMES, D. C. In Perspective of the Costochondral Syndrome in the Auscultation of Chest Pain. *JAMA* 156:1744, 1954.

- BERNSTEIN A., and WHITE F Z Unusual Physical Findings in Pleural Effusion Intrathoracic Manometric Studies *Ann Int Med* 37 73 1952
- BERSON W and ADRIANI J Silent Regurgitation and Aspiration During Anesthesia *Anesthesiology* 15 644 1954
- BIRD H Talking with Patients *Ann Pract* 6 270 1955
- BURCHELL H H Symposium on Dyspnea Introduction *Proc Staff Meet Mayo Clinic* 27 49 1955
- CANNON H R The Changing Pathologic Picture of Infection Since the Introduction of Chemotherapy and Antibiotics *Bull New York Acad Med* 31 87 1955
- CAFFEY J A Pain from the Pleura and Pericardium *Research Publ A Ner & Ment Dis*, 23 263 1943
- DOLL R and HILL A B A Study of the Aetiology of Carcinoma of the Lung *Brit Med J* 2 1278 1952
- DUSTAN H P, TAYLOR R D, CONCORDIA A C and PAGE I D Rheumatic and Febrile Syndrome During Prolonged Hydralazine Treatment *JAMA* 154 23 1954
- EVANS J A Roentgen Observations of the Aging Chest *J Am Geriatr Soc* 2 772 1954
- FULCHUM C H Epidemic Pleurodynia *JMA Georgia* 31 63 1942
- GRAESER J M W L C and ROBERTSON O H Physical Signs and Roentgenographic Findings in Lobar Pneumonia *Arch Int Med* 53 49 1914
- GREENE J A Unusual Sounds Emanating from the Chest *Arch Int Med* 71 410 1943
- HERRMANN G R Clinical Case Takings *Supplements to Methods in Medicine* 2nd ed St Louis C V Mosby Co 1940
- HLEPER W C Carcinogens and Carcinogenesis *Am J Med* 8 355 1950
- ISSELBACHER K J, KLAUS H., and HARDY A L Asbestos and Bronchogenic Carcinoma *Am J Med* 15 771 1953
- JÄRVINEN K A J and KUMLIN T Carcinoma of the Lung Smulating Early Rheumatoid Arthritis *Ann Rheum Dis* 13 52 1954
- KERR A JR, and DERRIS V J The Syndrome of Cough Syncope *Ann Int Med*, 39 1740 1953
- LANSBURY J and ROGERS F B The Hydralazine Syndrome *Bull Rheumat Dis*, 5 85 1955
- MORROW J D, SCHROEDER H A and PERRY H M Jr Studies on the Control of Hypertension by Hypophy II Toxic Reactions and Side Effects *Circulation* 8 878 1951
- PATERSON R H Cervical Ribs and the Scalenus Muscle Syndrome *Ann Surg*, 111 531 1940
- PERRY H M., and SCHROEDER H A Syndrome Smulating Collagen Disease Caused by Hydralazine (Aprosol ne) *JAMA* 154 670 1954
- POTTINGER F M Auscultation *Am Rev Tuberc*, 56 1 1947
- REINMAN H A Periodic Disease *Medicine* 30 719 1951
- ROCHE J., and SHIMON F G Epidemic Pleuritic Pain A Review of 17 Cases in a Military Camp *India Command Brit M J* 2 157 1946
- ROGERS A C T., and BOGEN E The Rise and Fall of Physical Examination in the Diagnosis of Diseases of the Chest *Dis Chest* 22 478 1952
- ROSE E., and EDEIKEN J The Association of Nodular Goiter with Thoracic Pain *Ann Int Med* 34 1126 1951
- SOSVIAN M C Fashions in Medicine and in Medical Education *Harvard Med Alum Bull* October 1954
- WARTENBERG R *Introduction to Diagnostic Tests in Neurology* Chicago Year Book Publishers 1953
- WEIRHAECHER W H Significance of Tietze's Syndrome in Differential Diagnosis of Chest Pain *JAMA* 157 505 1951
- WHITTY C W M On so called Laryngeal Epilepsy *Brain* 66 43 1943
- WYNDER E L., and GRAHAM E A Tobacco Smoking as a Possible Etiologic Factor in Bronchogenic Carcinoma *JAMA* 143 329 1950
- WILLIAMS N Cough Fracture of the Ribs Unassociated with Pulmonary Tuberculosis *Brit M J*, 2 1494 1951

The Chest X-Ray: Anatomical and Technical Considerations

Introduction

SINCE THE DETECTION of pulmonary lesions especially those occurring in the course of systemic diseases, depends almost exclusively on the chest x ray findings, it is in order to dilate on this aspect of the problem. The following pages will deal chiefly with normal anatomy and developmental anomalies with special reference to such features which come into consideration in differential diagnosis. The more important technical procedures will be defined briefly. It is

beyond the scope of this book to enter into technical details which are adequately covered in standard works on the subject. The chapter to follow will be devoted to the limitation and pitfalls of roentgen diagnosis, a matter of great concern to the clinician and one not sufficiently appreciated by the roentgenologist because of his limited contact with the patient and the specific problem under consideration.

Normal Anatomy and Developmental Anomalies

THORACIC CAGE

The cavity containing the lungs consists of bony and soft structures. The former includes ribs, sternum, clavicles, scapulae, spine and the upper parts of the humerus, the latter includes muscle, breasts and the lower portion of the cervical region. One needs to be familiar with the topographic anatomy of the chest and its contents to be able to differentiate shadows which fall within the 'normal' range from those caused by disease (Figure 72).

Ribs

Locating and counting correctly the ribs is an important step in localizing disease. The first rib articulates with the first vertebral body, the lower ribs, between successive bodies. The upper articulations of each vertebral body therefore corresponds to the number of the rib attached to it. The anterior articulation of the first costal cartilage is covered by the sternal end of the clavicle. The angle formed by the manubrium and sternum is the site of articulation of the second rib, a landmark in counting ribs anteriorly.

Each interspace is numbered by the rib above. The prominence of the seventh cervical spine facilitates the counting of vertebrae and ribs on the posterior surface of the chest. Because of the downward slope of the spinous processes, the downward slope of the chest corresponds to the level of the vertebral body beneath it. The downward slope of the ribs, from back to front, makes the level of the tenth rib posteriorly to correspond approximately to the level of the sixth, or even fifth rib, anteriorly.

The physique of the individual and the phase of respiration in which the chest x ray is taken have considerable bearing on the position of the anatomic landmarks. In the presence of emphysema, the ribs assume a more horizontal position giving rise to a barrel-shaped chest, in pleuro-pulmonary fibrosis, the ribs are drawn together on the side of the major involvement. Scoliosis of the spine results in asymmetry of the two sides of the chest and dislocation of organs. Pectus excavatum may occasionally be suspected in the postero-anterior film by the dislocation of the heart to the left.

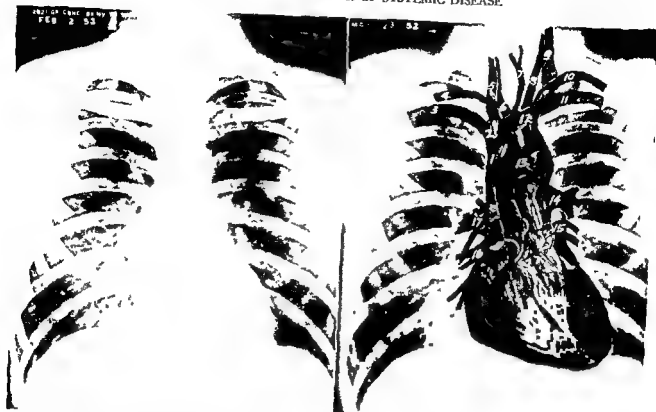


Figure 72 Relation of heart and great vessels to pulmonary structures A (Left) Chest x ray of a healthy adult B (Right) Heart and great vessels superimposed on chest x ray 1 superior vena cava 2 right innominate vein 3 right subclavian vein, 4 right subclavian artery, 5 right internal jugular vein, 6 innominate artery, 7 inferior thyroid veins, 8 left common carotid artery, 9 left internal jugular vein, 10 left subclavian artery, 11 left subclavian vein 12 left innominate vein 13 arch aorta 14 left pulmonary veins 15 left pulmonary artery, 16 right pulmonary artery 17 right pulmonary veins

(Drawn by Jessica Holden after Richard C Matthias Department of Visual Education Baylor University College of Medicine, Houston, Texas)

Developmental anomalies of ribs are quite frequent. They may be associated with malformation of adjoining vertebrae. The first rib may be rudimentary and abnormally shortened. The anterior portions of the upper ribs may be forked or fused, at times simulating cavity in the lung. An accessory (cervical) rib occasionally articulates with the seventh cervical vertebra on one or both sides. Cervical ribs occur more often on the left side but symptoms are usually more pronounced if they occur on the right side for the reason that most individuals are right handed and there is greater hypertrophy of the attached muscles. In the young, symptoms referable to cervical ribs are rarely encountered. After puberty and completion of rib growth, cervical ribs may cause nervous, vascular or muscular symptoms due to pressure on the subclavian ar-

tery or the brachial plexus. It is claimed that the, so called, cervical rib syndrome is more often caused by an unusually wide attachment of the scalenus anticus muscle rather than by the rib itself.

Soft Structures

The folds of skin and muscle projecting in the chest x ray may be a source of misinterpretation. A faint linear shadow produced by a fold of skin is often seen running parallel with the upper border of each clavicle. Giant emphysematous blebs may cause an abnormal degree of translucency of one or both upper lobes. The latter may be seen with the naked eye as soft masses bulging through the anterior triangles of the neck. The same applies to cervical hernias of the lungs, unilateral or bilateral, which may

protrude through the superior aperture of the thorax. The site of herniation is between the sternocleidomastoid and scalenus anticus muscles in Sibson's fissure which normally limits the excursion of the pleura and lung.

Well developed muscles of the chest, back and neck may interfere with the translucency of the lungs. In thin individuals the muscle planes may be distinguishable. The sternomastoid often obscures the apical lung field more so on the side to which the head is turned. Large pendulous breasts decrease the illumination of the lower lung fields and may show their margins in the chest x-ray, absence of a breast after mastectomy or as a result of underdevelopment causes hyperillumination. Darkly pigmented or prominent nipples in thin individuals often project as circular opacities simulating metastatic lesions. The superior vena cava and innominate vein form the right border of the superior mediastinum the shadow of the latter often infringing on the inner aspect of the right upper lobe especially if the patient is not centered properly.

DIAPHRAGM

This muscle arches in two leaves the dome of each projecting into a corresponding hemithorax at a higher level on the right than on the left. The inclusive height of the diaphragm is measured at the level it reaches on the right side near the spine. This usually corresponds to the level of the tenth dorsal rib in midrespiration. In the lateral projection the inferior portion of each leaf reaches the higher level the posterior portion making a sharp curve downward. In obese persons especially one may find a well defined triangular shadow at one or the other costophrenic angles more often the left. The shadow has a rather soft density and represents an extrapericardial collection of fat. In the lateral projection the density cast by the pad of fat is seen to lie anteriorly adjacent to the sternum. Such shadows are often a source of confusion requiring additional diagnostic procedures including a complete gastrointestinal visualization and a barium enema to rule out a peristernal diaphragmatic hernia through the foramen of Morgagni as well as congenital pericardial cysts

and diverticula. Bronchoscopy and bronchography may also be indicated to rule out carcinoma.

The posterior recess of the diaphragm is quite deep and accommodates several hundred cc of fluid an amount insufficient to be detected in a conventional P-A chest x-ray. It should be noted that an infrapulmonary pleural effusion may simulate a high diaphragm. Friedman collected seventeen such cases in a relatively short time. The induction of a pneumoperitoneum is a useful diagnostic and if the fluid is on the right side insufflating the stomach with citrocarbonate or a Seidletz powder will accomplish the same purpose on the left side.

The vertebral portion of the diaphragm is of particular interest because this part is pierced by openings through which pass the esophagus, aorta, vena cava, azygos vein and thoracic duct, as well as the vagus and sympathetic nerves. The diaphragmatico-esophageal membrane and the loose attachment of the peritoneum constitute a vulnerable site for hiatus hernias. Barium examination for diaphragmatic hernia is important in every gastrointestinal examination. The symptoms of diaphragmatic hiatus hernia may simulate those of angina pectoris, gallbladder disease, duodenal ulcer and carcinoma of the terminal esophagus or cardia of the stomach. Unexplained anemia and intractable cough may be caused by hiatus hernia. The frequent occurrence of a pleural effusion in a costophrenic sinus as part of a systemic disease has been mentioned repeatedly in these pages.

Occasionally there is noted a double contour of the right leaf of the diaphragm more evident in the lateral projection. The bulge is due to the pushing upward of a mass of liver and may simulate a tumor (Figure 49). Richman and Barry reported four such cases two having been referred with a diagnosis of tumor and one with that of subdiaphragmatic abscess. One of the patients was submitted to exploratory thoracotomy before the diagnosis was established. However a thoracotomy should rarely be necessary. A diagnostic pneumoperitoneum will reveal a layer of air between diaphragm and liver and help clarify the situation. Other features in the

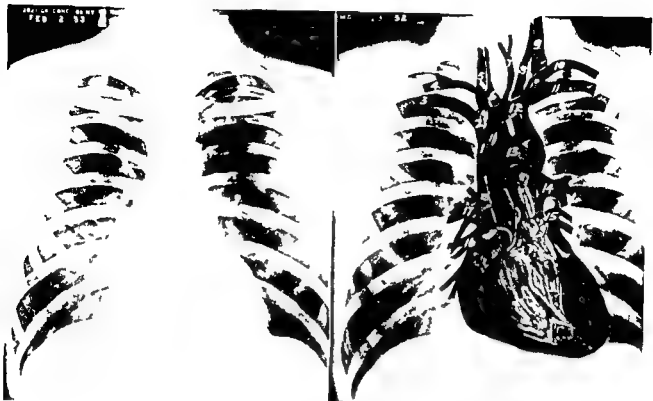


Figure 72 Relation of heart and great vessels to pulmonary structures A (Left) Chest x ray of a healthy adult B (Right) Heart and great vessels superimposed on chest x ray 1 superior vena cava 2 right innominate vein 3 right subclavian vein 4 right subclavian artery 5 right internal jugular vein 6 innominate artery 7 inferior thyroid veins 8 left common carotid artery 9 left internal jugular vein 10 left subclavian artery 11 left subclavian vein 12 left innominate vein 13 arch aorta 14 left pulmonary veins 15 left pulmonary artery 16 right pulmonary artery 17 right pulmonary veins

(Drawn by Jessica Helden after Richard C. Wirthis Department of Visual Education Baylor University College of Medicine Houston Texas)

Developmental anomalies of ribs are quite frequent. They may be associated with malformation of adjoining vertebrae. The first rib may be rudimentary and abnormally shortened. The anterior portions of the upper ribs may be forked or fused at times simulating cavity in the lung. An accessory (cervical) rib occasionally articulates with the seventh cervical vertebra on one or both sides. Cervical ribs occur more often on the left side but symptoms are usually more pronounced if they occur on the right side for the reason that most individuals are right handed and there is greater hypertrophy of the attached muscles. In the young symptoms referable to cervical ribs are rarely encountered. After puberty and completion of rib growth cervical ribs may cause nervous, vascular or muscular symptoms due to pressure on the subclavian ar-

tery or the brachial plexus. It is claimed that the so called cervical rib syndrome is more often caused by an unusually wide attachment of the scalenus anticus muscle rather than by the rib itself.

Soft Structures

The folds of skin and muscle projecting in the chest x ray may be a source of misinterpretation. A faint linear shadow produced by a fold of skin is often seen running parallel with the upper border of each clavicle. Giant emphysematous blebs may cause an abnormal degree of translucency of one or both upper lobes. The latter may be seen with the naked eye as soft masses bulging through the anterior triangles of the neck. The same applies to cervical hernias of the lungs unilateral or bilateral which may

protrude through the superior aperture of the thorax. The site of herniation is between the sternocleidomastoid and scalenus anticus muscles in Sibson's fissure which normally limits the excursion of the pleura and lung.

Well developed muscles of the chest back and neck may interfere with the translucency of the lungs. In thin individuals, the muscle planes may be distinguishable. The sternum itself often obscures the apical lung field more so on the side to which the head is turned. Large pendulous breasts decrease the illumination of the lower lung fields and may show their margins in the chest x-ray, absence of a breast after mastectomy or is a result of underdevelopment causes hyperillumination. Darkly pigmented or prominent nipples in thin individuals often project as circular opacities simulating metastatic lesions. The superior vena cava and innominate vein form the right border of the superior mediastinum the shadow of the latter often infringing on the inner aspect of the right upper lobe especially if the patient is not centered properly.

DIAPHRAGM

This muscle arches in two leaves the dome of each projecting into a corresponding hemithorax at a higher level on the right than on the left. The inclusive height of the diaphragm is measured at the level it reaches on the right side near the spine. This usually corresponds to the level of the tenth dorsal rib in midrespiration. In the lateral projection the anterior portion of each leaf reaches the higher level the posterior portion making a sharp curve downward. In obese persons especially one may find a well defined triangular shadow at one or the other costophrenic angles more often the left. The shadow has a rather soft density and represents an extrapericardial collection of fat. In the lateral projection the density cast by the pad of fat is seen to lie anteriorly adjacent to the sternum. Such shadows are often a source of confusion requiring additional diagnostic procedures including a complete gastrointestinal examination and a barium enema to rule out a paraesophageal hernia through the foramen of Morgagni as well as congenital pericardial cysts

and diverticuli. Bronchoscopy and bronchography may also be indicated to rule out carcinoma.

The posterior recess of the diaphragm is quite deep and accommodates several hundred cc of fluid in amount insufficient to be detected in a conventional P-A chest x-ray. It should be noted that in infrapulmonary pleural effusion may simulate a high diaphragm. Friedman collected seventeen such cases in a relatively short time. The induction of a pneumoperitoneum is a useful diagnostic aid if the fluid is on the right side insufflating the stomach with citrocarbonate or a "cellulose" powder will accomplish the same purpose on the left side.

The vertebral portion of the diaphragm is of particular interest because this part is pierced by opening through which pass the esophagus, aorta, vena cava, azygos vein and thoracic duct, as well as the vagus and sympathetic nerves. The diaphragmatic esophageal membrane and the lower attachment of the peritoneum constitute a vulnerable site for hiatus hernia. Barium examination for diaphragmatic hernia is important in every gastrointestinal examination. The symptoms of diaphragmatic hiatus hernia may simulate those of angina, pectoris, gallbladder disease, duodenal ulcer and carcinoma of the terminal esophagus or cardia of the stomach. Unexplained anemia and intractable cough may be caused by hiatus hernia. The frequent occurrence of a pleural effusion in a costophrenic sinus, as part of a systemic disease has been mentioned repeatedly in these pages.

Occasionally there is noted a double contour of the right leaf of the diaphragm more evident in the lateral projection. The bulge is due to the pushing upward of a mass of liver and may simulate a tumor (Figure 49). Richman and Barry reported four such cases two having been referred with a diagnosis of tumor and one with that of subdiaphragmatic abscess. One of the patients was submitted to exploratory thoracotomy before the diagnosis was established. However a thoracotomy should rarely be necessary. A diagnostic pneumoperitoneum will reveal a layer of air between diaphragm and liver and help clarify the situation. Other features in the

differential diagnosis of an abnormally elevated diaphragm are discussed in Chapter 10

In the presence of advanced emphysema or pneumothorax, the insertion of the costal components of the diaphragm are sometimes seen as step-like irregularities. The latter are brought out best in the inspiratory position. An uneven pull of the pericardial ligaments may also produce irregularities of the muscle. The diaphragm is often fixed at one or both costal margins by pleural adhesions with obliteration of the normally clear costophrenic sinuses.

MEDIASTINUM

The mediastinum and its contents cast the central shadow in the chest x-ray. The space is bounded mesially by sternum, posteriorly, by the spine and below by the diaphragm. Prior to the widespread utilization of roentgenography and thoracic surgery, the mediastinum was a relatively unexplored region. But with the introduction of methods of precise localization and safe exploration, the mediastinum has assumed considerable importance. Nonetheless, a differential diagnosis of disease within the space still presents many difficulties.

In the lateral projection, the one necessary for proper delineation of the space, the mediastinum is seen to consist of three compartments in relation to its chief contents: the pericardial sac and heart. The anterior mediastinum is an illuminated space between the sternum and pericardium and contains the thymus or its remains, and the anteromesial projections of the lungs. This space also contains lymph nodes, fat areolar tissue and branches of the internal mammary artery. The major abnormalities which may affect the retrosternal region or the anterior mediastinum are tuberculosis of the chondrosternal and chondrocostal junctions which may give rise to cold abscesses of the chest wall. Tumors of the sternum or costal cartilages are rare. The anterior mediastinum is also the site of intrathoracic substernal thyroid, simple enlargements or neoplasms of the thymus gland including mediastinal lipomas, dermoid cysts and teratoid tumors originating in congenital rests. Tumors of lymphatic origin including the

lymphomas, lymphosarcoma and Hodgkin's disease, as well as cystic tumors, are also most often found in the anterior mediastinum.

The middle mediastinum, the dense portion of the space, contains the heart and the point of origin of the great blood vessels. The phrenic nerves run through this space. The more important abnormalities affecting the middle mediastinum are obviously those associated with diseases of the heart and major blood vessels.

The posterior mediastinum, an illuminated space between the heart and spine, contains the trachea and main bronchi, esophagus, the thoracic portion of the descending aorta, azygos and hemiazygos veins, thoracic duct, vagi, sympathetic and splanchnic nerves. Bronchogenic cysts are found at points of bifurcation of the trachea and major bronchi. The tracheobronchial lymph nodes occupy the angles between the trachea and each bronchus; the bronchopulmonary lymph nodes are found at the root of each lung. These structures are often the site of metastatic disease. This region is the favored site of neurogenic tumors originating in spinal intercostal or sympathetic nerves.

The region immediately above the aforementioned three compartments is the superior mediastinum. Anatomically, the latter lies between the manubrium sterni anteriorly and the upper four thoracic vertebrae posteriorly. But inasmuch as the major structures occupying this region continue into the posterior mediastinum, the superior and posterior divisions are, for practical purposes, considered as one. The superior mediastinum contains the aortic arch and great vessels, the innominate veins and superior vena cava, trachea, esophagus, thoracic duct, thymus as well as the phrenic, vagi and left recurrent nerves. As mentioned, the superior mediastinum is a frequent site of suppuration originating in the throat, spine and esophagus.

Superior Vena Caval Obstruction

Obstruction of the superior vena cava may be found in association with malignant lymphomas, metastatic carcinoma and other systemic diseases. The major causes of caval obstruction are aortic aneurysms, bronchogenic carcinoma

with mediastinal involvement and thrombosis (Figure 73). In 1934 Thirlich and co-workers reviewed the literature and compiled 309 reported cases. In 1949 Hinshaw collected in addition 127 cases. The obstruction may be complete or incomplete. The location and extent of the collateral circulation depends upon the site of obstruction and completeness of the obstruction. Katz and co-workers found by means of phlebography with diodrast that if the site of occlusion of the superior vena cava is above the point of entrance of the azygos vein the latter and its tributaries are the main collateral channels and therefore visible collateral circulation is not extensive. A few dilated veins may be seen in the neck, shoulder regions and upper part of the chest. If the obstruction is below the azygos vein an extensive collateral circulation is visible in the chest, back, groin and abdominal wall representing anastomosis between the superior and inferior vena caval system.

Obstruction of the superior vena cava below the entrance of the azygos vein is tolerated with much more difficulty because the blood has to take a circuitous route by way of the inferior vena cava to reach the heart. Additional diagnostic criteria of obstruction of the superior vena cava are the demonstration of significantly elevated venous pressure (180 mm. water or above) in the upper half of the body in the presence of normal venous pressure in the lower half and the demonstration of a collateral circulation over the upper half of the body chiefly the front if the chest. The collateral circulation may be outlined by infrared photography and better still by phlebography. By means of the latter it is possible to demonstrate the point of obstruction or the presence of a mass or other lesion.

HILUS

The hilus is not a distinct space rather an eccentric wedge shaped depression in the medial surface of each lung. Through the hilus pass the various structures which make up the root of the lung. Although it is difficult to define what constitutes a normal hilus distinctly pathological states are usually evident if one makes due allowance for the age, occupation and previous lung

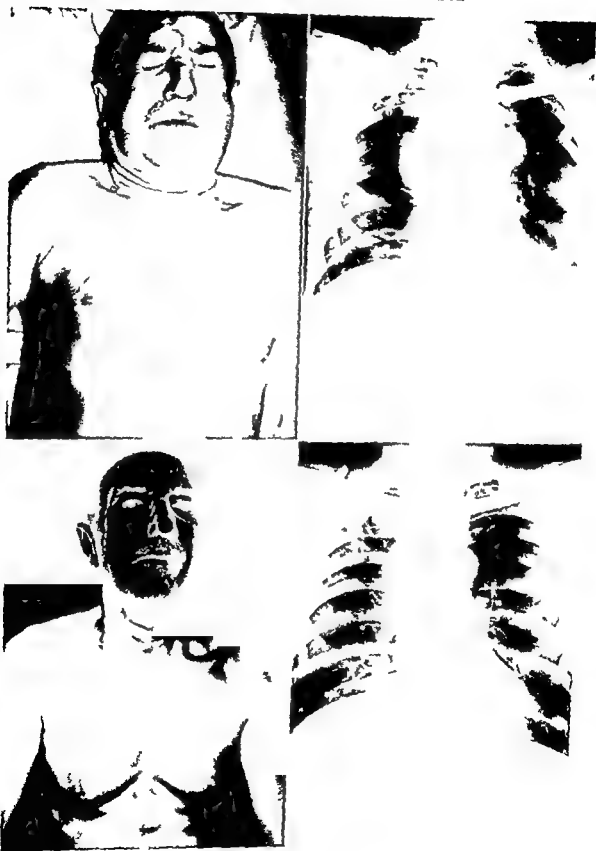
infections of the individual. The main hilar shadow is composed almost exclusively of the pulmonary artery and its major subdivisions and to a lesser degree veins. Normal bronchi do not cast shadows in the chest x-ray, nor does the hilar vessel densities cast by bronchopulmonary lymph nodes unless they are involved in a diffuse lymphatic process. Occasionally one sees adjacent to the hilus one or more oval translucent areas cast by cross sections of large bronchi. Adjacent to these one may find similar densities representing blood vessels caught on end.

The important structures of the hilar region exclusive of the large blood vessels are the lymph nodes which drain the lungs and pleura. Systemic diseases notably the malignant lymphomas and sarcoidosis as well as generalized lymphohemogenous infections sooner or later involve the bronchopulmonary, tracheobronchial and paratracheal lymph nodes. The structures entering the hilus of each lung occupy the middle mediastinal space. Since the major occupant is the heart in the pericardial sac large neoplasms primary as well as metastatic involving this region are displaced anteriorly posteriorly or superiorly. The contents of these mediastinal spaces are visualized in lateral chest x-ray projections. With the marked increase in the use of chest roentgenography and the recent advances in thoracic surgery these several compartments of the mediastinum have assumed tremendous importance. What was once unexplored "No Man's Land" is now "Main Street".

LUNGS AND FISSURES

The lungs lie freely in the pleural cavities attached only at the root and by the pulmonary ligaments. Each organ is conical in shape assuming the configuration of the cone in which it is confined. The right lung is slightly larger, shorter and wider than the left due to the greater bulk of the right lobe of the liver and the left sidedness of the heart. The volume ratio of the right lung is compared to the left is approximately 55:45. The lungs are marked by surface impressions corresponding to the position of the ribs, heart and large blood vessels. Each organ has an apex base, three surfaces and two margins. The right lung has two fissures which divide the organ

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE



(See legend on opposite page)

three lobes. The left lung has one fissure dividing the organ into two lobes. Quite often the horizontal fissure dividing the upper and middle lobes is either incomplete or absent in important consideration in the surgical treatment of disease. The parenchyma of the lung is characterized roentgenologically by a delicate webbing composed chiefly of vascular elements. The striations are densest in the inner and lower lung fields. The translucency of the organs varies in its vertical plane i.e. from hilus outward. Moderate emphysema accentuates the vascular markings and advanced emphysema obliterates them.

Developmental Anomalies

There may be a congenital absence (aplasia) of a lung (Figure 74 A) or varying degrees of defective development (hypoplasia). The roentgen features which distinguish these conditions from acquired disease are found in the frequent coexistence of structural defects of the trachea, bronchi and blood vessels, the symmetry of the thoracic cage and the absence of hypertrophy of the right side of the heart. In 1910 Ingram and co-workers collected from the literature the reports of fifty-five proved cases of aplasia of the lung including sixteen in which the diagnosis was made during life. These investigators reported two additional cases of aplasia of the lung diagnosed during life. In one a corroborative angiocardioradiographic examination revealed a single pulmonary artery. They noted that the condition is usually asymptomatic and discovered accidentally. It occurs more frequently in males and three times as often on the left side as on the right.

Situs Inversus and Bronch ectasis (Kartagener's Syndrome). In recent years the elements of bronchial obstruction and infection have been rightly endowed with much greater importance in the development of bronchiectasis than the possible factor of a congenital weakness of the respiratory tract. In occasional cases however

bronchiectasis may be due to failure of broncholar canalization during embryogenesis causing arrested development of corresponding bronchopulmonary segments. Instances of situs inversus and bronchiectasis lend support to this belief. Although the association of complete transposition of the viscera with bronchiectasis was noted previously, Kartagener in 1933 was the first to point out the greater frequency of bronchiectasis with sinusitis in persons with situs inversus. Situs inversus occurs in approximately 1 in 8,000 persons, bronchiectasis in about 20 per cent of persons with situs inversus.

Kartagener's syndrome is an inherited anomaly and is often associated with developmental defects of other parts of the body. Olsen found that eleven of eighty-five patients with situs inversus had congenital anomalies of the heart, hydrocephalus, imperforate anus, cleft palate, flail thumb and accessory digits. Other investigators have also noted a high incidence of congenital malformations in association with Kartagener's syndrome. The vast majority of patients with this condition are discovered in infancy. Bergstrom and co-workers reported a family in which there occurred among six siblings two cases of transposition of viscera, sinusitis and bronchiectasis as well as other anomalies and two of bronchiectasis without situs inversus. These authors tribulated the reports of eighty cases of Kartagener's syndrome previously reported. The following is a classical example.

Case 32 Male—Age 22

The patient was admitted to the Morrisania City Hospital with fever, chills and productive cough. The story was that he had been treated since youth for sinusitis, repeated seizures of bronchitis and bronchopneumonia. On a previous admission to the Morrisania City Hospital the patient was found to have situs inversus. Of interest in the family history was the fact that the patient's father, who had died

Figure 73 Superior vena caval obstruction. A (Upper left) Marked swelling of face, neck and chest on engorgement of blood vessels of upper chest and shoulder. B (Upper right) Considerable widening of superior mediastinum, rounded masses extending into adjacent lungs, scattered infiltrations in right upper lobe. C (Lower left) After radiotherapy, marked reduction in swelling of face and neck, vascular pattern less prominent. D (Lower right) Considerable decrease in superior mediastinal density. (Biopsy of lymph node revealed malignant lymphoma.)



Figure 74 Developmental bronchopulmonary anomalies. A (Left) Homogeneous density obscuring entire left hemithorax; heart and mediastinum displaced to the left. (Agencies of left lung in an infant; also cervical spina bifida on bronchoscopy; only the left main bronchus was visualized; bronchography failed to reveal iodized oil in the left bronchial tree.) B (Right) Delicate line extending to the apical pleura from a bulbous end at the upper mediastinum giving appearance of an inverted comma. (Azygos lobe in a child.)

of tuberculosis four years previously; also had dextrocardia.

The physical, chest x-ray and laboratory findings revealed a pneumonia in the right upper lobe. In addition the chest x-ray showed a complete dextrocardia (Figure 75A). The frontal sinuses were rudimentary. The ethmoids and maxillary sinuses showed marked opacification suggestive of exudate. Bronchography revealed extensive dilatation of the bronchi in both lower lobes, more marked on the left side (Figure 75B). The patient responded to antibacterial treatment and was discharged to the Chest Clinic with the plan that when the infection cleared completely it might be feasible on some future date to treat the patient's bronchiectasis surgically.

Azygos Lobe. A fairly frequent developmental anomaly is the finding of a split upper lobe. The malformation is due to an abnormal position of the azygos vein during its embryologic development. Instead of entering the superior vena cava posteriorly at the hilus, the azygos vein runs laterally, arches over and bisects

the upper lobe. The septum dividing the lobe consists of two layers of parietal pleura and two layers of visceral pleura since the azygos vein lies extrapleurally. The vein lies at the base of the septum. The roentgen appearance of the azygos lobe is featured by the presence at its lower margin of a thin, delicately curved line extending from the chest wall to the upper mediastinum. The line ends in a rounded density mesially, the site of the azygos vein. The appearance of the line is likened to that of an inverted comma (Figure 74B).

Ellis and Bruwer noted that on occasion the azygos vein may cast a shadow in the chest x-ray which may be misinterpreted as a mediastinal tumor. Several instances are cited where exploratory thoracotomy had been carried out in which a mediastinal shadow was actually due to a dilated azygos vein. Cases are also on record of pneumonia and tuberculosis limited to the azygos lobe. Enlargement of the density cast by the azygos vein may be noted in cases of su-

perior vena caval obstruction inferior vena caval obstruction portal hypertension and heart failure

Inferior Accessory Lobes One may encounter inferior accessory lobes which appear as areas of increased density or illumination depending on the state of the parenchyma. Rigler and Erickson quote Schaffner who found at postmortem examination partially or entirely formed inferior accessory lobes in no less than 45.7 per cent of 210 human lungs. In the chest x-ray the interlobar septum demarcating an inferior accessory lobe is seen as a fine linear shadow extending from the medial portion of the diaphragm upward and mesially toward the hilum. The diaphragm may show a triangular dimpling at the point of origin of the fissure.

Bronchovascular Anomalies Of current interest is the occasional finding of a so-called intralobar sequestration of the lung. Price and co-workers described eight examples and Wainman and Tyler reported seven additional surgically and pathologically proved cases. Isolated case reports have been published by others. It would seem that intrapulmonary sequestration is not

rare and will probably be encountered more often once the condition is better recognized.

Intralobar sequestration is associated with one or more abnormal arteries arising from the lower thoracic or upper abdominal aorta or some other vessel. Such anomalous arteries have the same histological structure as the aorta containing a relatively large amount of elastic tissue and being subject to atheromatous changes due to systemic pressure variations. Anomalous arteries carrying oxygenated blood from the aorta may enter normally placed lung tissue in which case they are more commonly encountered on the right side and may be bilateral. The most common site of origin of anomalous pulmonary arteries is from the descending aorta above the level of the diaphragm and in relation to the inferior pulmonary ligament.

The ectopic mass of lung tissue does not usually connect with the bronchial tree but is attached to a blind bronchus. In case of the latter the sequestered mass is devoid of carbon pigment. The sequestered portion of lung may be composed of normal tissue or may be bronchiectatic or cystic. The mass may lie within the



Figure 75 Case 32 Situs inversus and bronchiectasis (Kartagener's syndrome). A (Left) Dextrocardia soft infiltrate on right upper lobe. B (Right) Bronchogram shows extensive bronchiectasis, more marked on left. Air containing stomach is seen faintly beneath right leaf of diaphragm. X-rays showed rudimentary frontal sinuses and a pacific on of ethmoids and maxillary sinuses.)

lower lobe or adjacent to the left lower lobe. At times, the sequestered lobe or lung may appear as a giant cyst. Accessory lobes, in contradistinction to intralobar sequestrations, are entirely separate from the parent mass and the supplying pulmonary artery and veins arise normally from the hilus. Lower accessory lobes are sometimes referred to as extralobar sequestrations. A congenital diaphragmatic hernia may coexist. Almost invariably, extralobar sequestrations are found on the left side, the intralobar form may be found on either side.

Bronchovascular anomalies are discovered accidentally or as a result of symptoms due to secondary infection. Infection is common in intralobar sequestration, the condition often appearing as pulmonary abscess, empyema, subdiaphragmatic hernia or bronchiectasis. It is important to be aware of the existence of intralobar sequestrations because in the resection of such masses, the surgeon has to be on guard lest he cut the artery or arteries communicating with the aorta. A number of deaths have been reported as a result of such accidents.

I have had under my observation three patients with intralobar sequestrations. A man of 27 was found to have a large, oval, circumscribed density showing several fluid levels in the region of the left lower lobe behind the heart. A cyst was suspected, but at operation, performed by Dr. Morris Rubin, an intralobar sequestration was discovered attached to a large artery which had pierced the diaphragm. The mass was excised successfully. The second patient, a girl of sixteen, was found to have a somewhat smaller rounded density at the right cardiophrenic angle. In this case, an intralobar sequestration was suspected prior to the operation and the surgeon warned that he might encounter an anomalous blood supply. This proved to be the case. At operation an aberrant artery was found originating above the level of the diaphragm. The mass was resected successfully and the patient made an uneventful recovery. Because of several unusual features associated with the following patient, a brief history of the case is worth citing.

Case 33 Male—Age 27

The patient became ill in 1931, at the age of nine years. He was admitted to a hospital in North Carolina and had a left-sided thoracotomy and rib resection for a presumed empyema. A draining sinus remained but the patient had no respiratory difficulties and was able to work at heavy manual labor. The patient cleansed and dressed the thoracotomy wound and reinserted the drainage tube when necessary. In 1940, the patient came to New York City and entered a city hospital with the hope of having the draining sinus eradicated. At this time the disease in the chest was ascribed to "an old draining abscess of the left lower lobe, but the possibility of an encapsulated hydropneumothorax could not be excluded." A thoracoplasty was done and the 7th, 8th, 9th and 10th ribs resected. A year later the patient reentered the same hospital for a revision thoracoplasty and in 1945 he returned for a third time and an additional attempt was made to obliterate the presumed empyema space with a Schede thoracoplasty. However, the patient was left with a large wall defect. He went back to work in a factory, caring for the wound himself.

When I saw the patient, in May, 1950, he had slight unproductive cough but otherwise few symptoms referable to the chest. Examination revealed an underweight Negro male with cyanosis and clubbing of the fingers and toes. There was a large defect in the left lateral chest wall measuring 7 x 7 centimeters (Figure 76C). The surrounding skin was extensively scarred as a result of previous operations. The interior of the defect showed the presence of a glistening membrane with numerous ridges and trabeculations. The membrane was very flexible and herniated through the chest opening on deep cough. At the apex of the space, there was a small opening which appeared to communicate with a bronchus. The remainder of the physical examination was noncontributory. The chest x-ray revealed extensive loss of bony thorax over the left lower chest due to previous thoracoplastic operations. The upper lobe was partly aerated. The right lung was clear, the heart displaced to the right (Figure 76A).

The patient was admitted to the Morrisania City Hospital on May 8, 1950. A congenital cyst of the lung was suspected and operation advised. At operation performed by Dr. Morris Rubin the left lung was found attached to the periphery of the large defect previously described. The defect was incised along its circumference to permit detach

ment from the chest wall. The muscle layers were then opened along the line of incision and a long segment of the lowest intercostal rib (5th) resected subperiosteally and the pleural cavity opened. The upper lobe was found to be free of adhesions. The lower lobe was completely replaced by a huge solitary lung cyst which had been misapicalized. The entire lung was mobilized by the separation of the lung cyst from its thoracic attachments.

A pneumonectomy was done by individual ligation of the pulmonary artery, superior and inferior pulmonary veins. The bronchus was isolated, clamped and cut and the stump closed with a single row of 0000 silk. The stump was then covered with adjacent pleura. Two aberrant arteries were found originating from the thoracic aorta entering the cyst wall. Both of these vessels were ligated and cut (Figure 76E).

In order to close the chest wall defect a thoraco-plasty was performed including segments of the 2nd, 3rd and 4th ribs. Part of the 2nd rib was left intact due to a congenital fusion with the 1st rib also because the patient's blood pressure had dropped. The soft tissues of the chest wall were then mobilized posteriorly to the dorsal spine and anteriorly to the sternum. It was possible to close the deoxygenated thoracic cage except for a small defect.

The postoperative course was uneventful except for an elevated temperature associated with a breakdown of the wound at the area of the previous operations. At that site there was necrosis of the skin which subsequently sloughed leaving a small opening. A draining sinus persisted for about three weeks and healed spontaneously. Sutures were removed during the second week postoperatively and the remainder of the wound healed by primary union in spite of the poor blood supply and tension at the suture line. The patient did well and was discharged. At first he noted dyspnea on exertion but it gradually disappeared (Figures 76B and D).

Interlobar Fissures

In considering the topographic anatomy of the fissures, a distinction needs to be made between the cadaveric and roentgen positions. Furthermore, one has to take into consideration the fact that the chest x-ray exposure is customarily made in inspiration. Tschman has drawn attention to the fact that the landmarks acquired at the dissection table are not necessarily applicable to the chest x-ray. He points

out, for example, that the bifurcation of the trachea is generally placed at the level of the intervertebral disc between the fourth and fifth thoracic vertebra, but in the chest x-ray taken in the upright position the bifurcation is considerably lower and undergoes shift with the respiratory cycle.

Brock has also drawn attention to the fact that the surface projections of the positions of the main interlobar fissures, as generally taught, are inaccurate being given at a higher level than is actually the case. The right main fissure ends at the costal pleura at least 4 cm. lower, or corresponding to the fifth rib near the vertebral column rather than to the level of the third thoracic spine and the fourth rib. The fissure follows the fifth rib until its costochondral junction and then slopes downward to the sixth rib. The interlobar fissure of the left lung leaves the vertebral column at a less definite point ranging from the level of the third to the fifth ribs sloping more vertically downward to reach the level of the seventh rib anteriorly.

Because of the obliquity of the main fissures and resulting overlapping of lobes it is obvious that only lateral projections of the thorax can show their slope; provided, of course, the fissures are discernible. The fissures are important structures not only because they form the boundaries of lobes but because they are potential spaces for fluid. The appearance of the lung margins at the fissure junctions may give a clue as to the state of the corticopleural layer of the organ as a whole.

The main interlobar fissure of each lung extends obliquely downward and forward from the front of the vertebral column to the sternum. The main fissure of the right lung gives off a secondary horizontal fissure in the posterior axillary line which runs anteriorly and slightly upward separating the upper from the middle lobes. The position of the horizontal fissure can be marked by a line drawn from the posterior axilla at the level of the fifth rib or interspace to the fourth costal cartilage. In the conventional postero-anterior view, the horizontal fissure is often found at the level of the third and as low as the fifth costal cartilages.



Figure 76 (See legend on opposite page)

Figure 76 Case 33 Bronchovascular anomaly intralobar sequestration in form of a giant cyst simulating emphysema A (Opposite page upper left) Extensive loss of bony thorax of left chest inferior

B (Opposite page lower left) Large oval defect of chest wall (interior of defect showed glistening membrane with numerous ridges) extensive scarring of skin from previous operations D (Opposite page, lower right) Appearance of chest wall after operation of large defect E Large solitary cyst showing many trabeculations



The right middle lobe is not in contact with the posterior chest wall. For practical purposes therefore physical findings elicited over the back of the chest from the base to the midaxillary level may be assumed to originate in the lower lobe, above it in the upper lobe. All the lobes excepting the right upper are in contact with the diaphragm. As a result disease of any lobe excepting the right upper, may cause pain not only in the chest but also in the abdomen. The anterior portion of the right horizontal fissure separating the right upper and middle lobes is often seen in the posterior anterior projection since the plane of the fissure is tangential to the central ray. The fissure here is usually at the level of the fourth rib. Because of the slight angula-

tion of the fissure the posterior interior view may show a parallel line below the fissure.

TERMINAL LUNG RADICLES

The air spaces through which gas exchange takes place make their appearance as small projections in the terminal respiratory bronchioles (Miller). The latter correspond to the ultimate subdivisions of the pulmonary artery which form vascular ducts about each lobule. Each primary lobule consists of a duct which leads by a number of ramifications to sacs the lining of which is composed of alveolar epithelium. The distal end of each alveolar duct is surrounded by a sphincter composed of muscle bands. Intercommunications have been shown to exist between alveoli

individual lobes allowing collateral circulation of air and fluid. These interalveolar pores play an important role in the spread of disease.

Many of the diseases described in these pages involve primarily or chiefly the terminal ridicles of the lungs. This applies not only to blood borne diseases or disease of the vascular system but also to pulmonary lesions associated with metabolic, hyperergic, hematologic and other disorders. The symptoms of anoxia, often encountered in these systemic diseases are frequently caused by an alveolar-capillary block interfering with the transfer of oxygen through thickened alveolar membranes.

BRONCHI AND BRONCHOPULMONARY SEGMENTS

The main bronchi arise in the trachea at the level of the fourth or fifth dorsal vertebrae, corresponding anteriorly to the second or third costal cartilages. The point of division, the carina, is a prominent ridge formed by fusion of tracheal and bronchial cartilages. Each main bronchus and its subdivisions permeate the lung in a tree like manner. The musculature of the bronchi consists of spiral and circular fibers which allow a rhythmic elongation and widening on inspiration and contraction on expiration. The bronchial cartilages disappear at the bronchioli, the latter being circular tubes composed of smooth muscle bands.

The right main bronchus, except for a slight lateral deviation of about 25°, is almost a direct continuation of the trachea. This anatomic continuity explains the predilection of the right lower lobe to aspiration pneumonia and foreign body lodgement. Possibly, too, the fact that most individuals are inclined to sleep on the right side is also a factor. The right main bronchus extends for a short distance from the carina and gives rise at an angle of about 90° to an upper bronchus supplying the right upper lobe. The main channel (intermediate bronchus) continues to a lower level at which point it gives off secondary divisions, at approximately the same level, to supply the middle and lower lobes. The left main bronchus gives off first one branch to the left upper lobe which immediately divides itself into two, one supplying the upper division of the

left upper lobe and the other, the lingula. A second major branch supplies the left lower lobe.

Inasmuch as many pathologic processes affect initially segments rather than complete lobes each of the latter is recognized as a composite of bronchopulmonary segments. A bronchopulmonary segment is an area of lung supplied by a relatively constantly placed bronchus, the orifice of which is situated in a large lobar bronchus and is visible to the bronchoscopist (Kramer and Glass). In localizing disease, the surgeon is particularly concerned with the segmental distribution of the bronchi and the projection of the latter on the surface of the chest. A number of attempts have been made to establish a bronchial nomenclature which can be used by bronchoscopists, roentgenologists, internists and surgeons.

The classification devised by Jackson and Huber, based on bronchoscopic and anatomic studies, has been accepted as the official nomenclature by a number of interested specialty groups. The principle arteries on each side are identified with the same nomenclature as that used for the bronchial segments. The bronchopulmonary segments cannot be considered as morphologic bronchovascular units because of the frequency with which blood vessels traverse one segment to the other. Table 8 gives the nomenclature of the

TABLE 8

NOMENCLATURE OF THE BRONCHIAL TREE AND CORRESPONDING BRONCHOPULMONARY SEGMENTS

Right Lung			Left Lung		
Lobes	No.	Division	Lobes	No.	Segment
Upper	1	Apical	Upper	11	Apical posterior
	2	Post. or		12	Ant. or
	3	Ant. or			
Middle	4	Lat. or Med. or	Lower	13	Superior
			(angular division)	14	Inf. or
Lower	5	Superior	Lower	15	Superior
	6	Med. or basal		16	Anterior (or basal)
	7	Ant. or basal		17	Lateral basal
	8	Lateral basal		18	Posterior (or basal)
	9	Post. or basal			
	10	Post. or basal			

From Jackson and Huber: *Dis. Chest* 9:319, 1943.

bronchial tree and corresponding bronchopulmonary segments, according to the Jackson-Huber classification (Figure 77).

The right middle lobe, lingula and the superior, also the basal segments of the lower lobes

ment additional comment because involvement of these parts often presents problems in diagnosis. To a considerable degree the difficulty lies in lack of precise knowledge of the anatomic and physiologic anatomy of these segments.

Right Middle Lobe

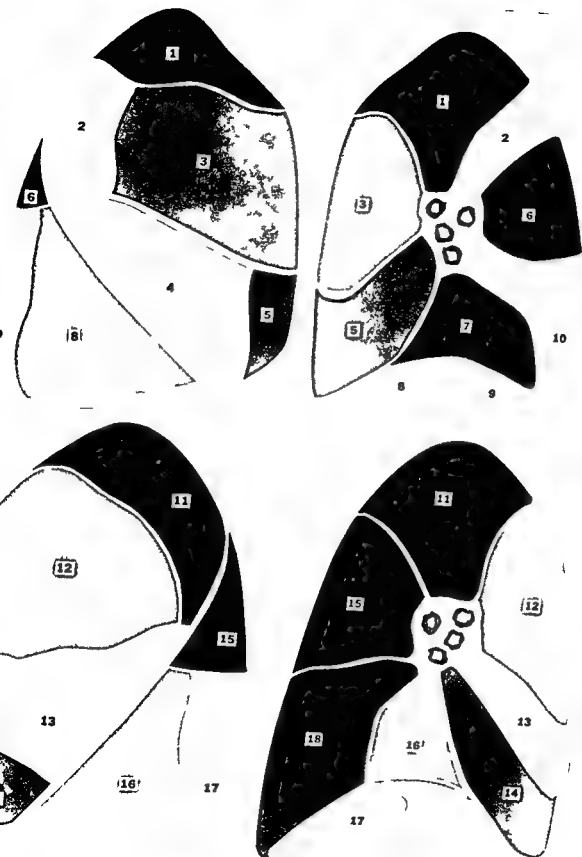
This lobe is separated from the right upper lobe by a horizontal fissure and from the lower lobe by an oblique fissure. Laterally the middle lobe is in contact with the lower anterior aspect of the chest medially with the right side of the heart and posteriorly with the lower lobe. The costal portion of the lobe is triangular in shape and the horizontal fissure is incomplete or absent in cases where the middle lobe is either partially or completely fused with the upper lobe. Because of the obliquity of the main fissure and the fact that the middle lobe lies anteriorly to the lower lobe roentgenologic study requires lateral as well as postero-anterior projection does not suffice for the additional reason that if the middle lobe is shrunk on it retracts to the hilus and its place is filled with overdistended lung. Although the lateral projection is obviously more revealing the contracted lobe may be obscured by densities cast by the heart and hilar structures. For these reasons an exact delineation of middle lobe disease often proves difficult.

The right middle lobe is composed of two bronchopulmonary segments one situated laterally the other medially. Either or both segments may be involved. Obstruction of the lateral (costal) division of the middle lobe bronchus is characterized in the P A projection by a diffuse cloudiness extending into the lower lung field a relatively clear zone separating the density from the right border of the heart. In the lateral projection the density appears triangular and is situated low and posteriorly. Obstruction of the medial (cardiac) division of the middle lobe bronchus produces in the P A projection an irregular density immediately adjacent to the right border of the heart. In the lateral projection the density appears quadrilateral lying immediately

behind the sternum and beneath the horizontal fissure.

In addition to the postero-anterior and lateral projections supplementary procedures are often necessary the most important being a lordotic view tomography and bronchography (Figure 78). The last mentioned is best combined with bronchoscopy because the diagnosis usually has to take into consideration a possible neoplasm especially in older age groups. The most frequent cause of contraction often associated with bronchiectasis of the middle lobe is a constricting collar of lymph nodes about the orifice of the right middle lobe bronchus. The roentgenographic appearance of a shrunk middle lobe or the right middle lobe syndrome may be simulated by interlobar pleurisy or pleuropneumothorax. A triangular density formed by the superimposed lower cardiac border and an elevated right leaf of the diaphragm and even a contracted depressed anterior segment of the right upper lobe may also simulate right middle lobe disease.

The vulnerability of the right middle lobe to cicatricial contraction of lymph nodes may be explained on anatomical grounds. Nelson Brock and others have shown that the bronchus to the right middle lobe more so than to any other lobe is subject to compression by enlarged lymph nodes which may cause atelectasis of the lobe. These investigators draw attention to the fact that the right middle lobe bronchus as it leaves the main chunnel forms an acute angle at the point of bifurcation the bronchus is surrounded by a chain of lymph nodes which drain the lymphatics not only of the middle lobe but also of the lower lobe. When these bronchopulmonary lymph nodes become enlarged, they are apt to exert pressure on the middle lobe bronchus. Should the bronchial channel become obstructed the lobe collapses leading in many instances to bronchiectasis. Bronchiectasis has been observed repeatedly in children who have gone through the primary infection with the tubercle bacillus especially in those who had signs of bronchial compression. In addition to shrunk and bronchiectatic the middle lobe may be the seat of pneumonia suppuration or neoplasm.



(See legend on opposite page)

Adler and co workers reported three cases of middle lobe disease due to histoplasmosis and one, to sarcoidosis

Lingula of the Left Upper Lobe

A counterpart of the right middle lobe is the lingula or the lower division of the left upper lobe. In a study of cleft upper lobes Boyden found that 8 per cent of left lungs exhibited a 'middle lobe' in various degrees of separation ranging from a true middle or lingular lobe to an ectopic arterial type. In health the lingula lies anteromedially, adjacent to left border of the heart. It is roughly triangular in shape the borders not well delineated. The lingula is supplied by the first branch of the left upper lobe bronchus and bifurcates into superior and inferior divisions. A diseased lingula may occasionally be seen in overexposed films as a dense mass behind the cardiac silhouette. Its exact definition requires left lateral projections, bronchography and the other procedures mentioned previously (Figure 79).

Superior Segments of Lower Lobes

From the nature of their embryologic development bronchial distribution and blood supply the lower lobes appear to be made up of two distinct parts. Each has two secondary bronchi one supplying the superior and posterior portion of each lobe, the other the basal portions. Occasionally the superior segment is separated by a well defined fissure. Disease limited to a superior bronchopulmonary segment of a lower lobe is projected in the hilar region in the P A chest x-ray. On the other hand disease affecting a basal bronchopulmonary segment is projected into a costophrenic sinus simulating a pleural effusion. Practically the entire superior segment lies behind the upper lobe of each lung. The basal

segments lie below the shadow of the diaphragm in the P A chest x-ray, therefore, only a small portion of the lower lobe is projected.

The status of a superior segment of a lower lobe is of prime importance in the treatment of disease especially tuberculosis for the reason that the superior segment is often involved in association with disease of an upper lobe or of the middle lobe. Tomography in the lateral as well as in the postero anterior projections are necessary to determine the condition of the superior segment of the lower lobe before resectional surgery is done. In addition to tuberculosis the superior segments are vulnerable to carcinoma and aspiration infections, including lung abscess.

Basal Segments of Lower Lobes

The major departure in the distribution of the basal segments of the right and left lower lobes is the combined anterior and medial segments of the left lower lobe into a single unit. In the postero anterior projection only the lowermost tips of the anterior basal segments are visible at the costodiaphragmatic sinuses. Collapse of the right lower lobe is particularly frequent because the supplying bronchus is in almost direct continuity with the main channel and as a result, foreign bodies and aspiration infections are apt to gravitate to that side.

Although the major roentgen features of a collapsed lower lobe are similar on both sides there are a few points of difference. Collapse of the right lower lobe often involves also the middle lobe because the origin of the two lobar bronchi are at approximately the same level. The fact that the atelectatic left lower lobe recedes behind the cardiac shadow prevents its recognition in the postero anterior projection. Lateral views are therefore necessary to delineate the atelectatic lobe. In some instances especially in

Figure 77A (Upper left) Bronchopulmonary segments right lung anterolateral view
Figure 77B (Upper right) Bronchopulmonary segments right lung medial view
Figure 77C (Lower left) Bronchopulmonary segments left lung anterolateral view
Figure 77D (Lower right) Bronchopulmonary segments left lung medial view

(For Nomenclature of Bronchopulmonary segments see Table 8)



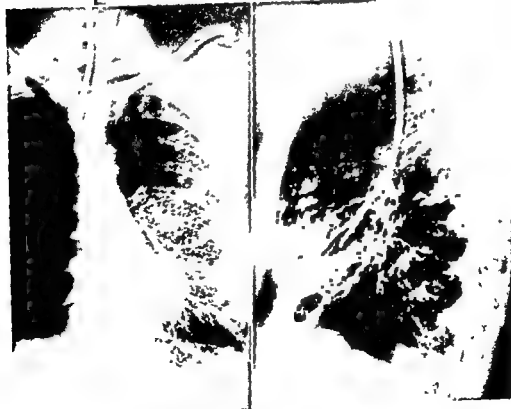
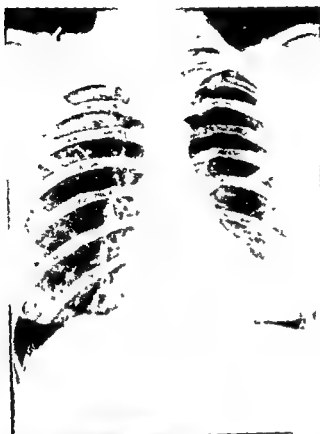
Figure 78 Demonstration of shrunk bronchiectatic right middle lobe. A Irregular density in region of right middle lobe. B Lordotic projection shows triangular density with a well demarcated lower border. (Continued on opposite page)

Figure 78C (Upper left) Right lateral projection shows irregular triangular density in region of right middle lobe. D (Upper right) Right lateral tomogram lateral section. Middle lobe appears as a sharply triangular density and somewhat quadrilateral in E (Lower left) medial section. F (Lower right) Bronchogram reveals middle lobe bronchi moderately ectatic. distal bronchi are free of oil. entire middle lobe appears dense and contracted. (Disease discovered accidentally in a forty four year old male. course featured by occasional mild respiratory infections.) (From Rubin and Rubin. *Dis. Chest*, 18:127, 1950)



(See legend on page 249)

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE



(See legend on opposite page)

over penetrated films the density of the collapsed lobe may be sufficiently radiopaque to be discernible behind the heart silhouette. In addition to the contraction of the involved mass collapse of a lobe is associated with distortion of the major interlobar fissures which are depressed and shifted posteriorly. In addition there is compensatory overdistention of the remaining lung as well as dislocations of the heart and mediastinum to one side or the other depending on the duration of the process and the presence or absence of an antecedent pleuritis.

Röntgen Techniques

The procedures available in the roentgen examination of the chest comprise two major steps (1) screening (fluoroscopy) and (2) photographing the fluorescent image on a sensitized film (roentgenography). The latter may be accomplished in one of a number of projections utilizing various penetration and contrast techniques.

Fluoroscopy

The place of this procedure in the detection of pulmonary disease depends to some extent on whether the examination is being conducted in the physician's office or in a hospital. In hospital practice the routine postero anterior chest x-ray serves as a scout film and fluoroscopy is utilized if the nature of the disease is not immediately apparent. The fluoroscopic examination enables also the preselection of additional procedures which may be necessary to arrive at a diagnosis. In office practice the fluoroscope is often the only x-ray apparatus available. The expert is able to glean considerable information from a fluoroscopic screening though less informed may obtain very little in fact so little that the examination may serve as a handicap by giving one a false sense of security. Under no condition can fluoroscopy serve as a substitute for roentgenography since small lesions and even large ones are easily overlooked. Furthermore fluoroscopy does not provide a permanent serial record which can be used in following the course of a disease. This in itself is of inestimable value in prognosis.

Felsen divides fluoroscopy into five phases which he designates as (1) observation (2) rotation (3) breathing (4) ingestion and (5) tilting. The first letters spell the word ORBIT which serves as a mnemonic. These phases are self explanatory. They serve to disclose detail space relationships displacements and vascular lesions. The last mentioned are brought out best through the Alvarez and Muller's maneuvers which have been described previously. By these maneuvers it is possible to increase or decrease intrathoracic pressure thereby changing the size of the vascular channel.

In the diagnosis of pulmonary lesions occurring in the course of systemic diseases fluoroscopy is seldom of much help excepting possibly in the diagnosis of pathological processes at the bases of the lungs which may be related to diaphragmatic or subdiaphragmatic disease. In this respect it should be mentioned that if the diaphragm is normally placed and is freely movable with respiration it is very unlikely that one is dealing with disease involving the muscle. The presence of discomfort during respiration associated with impediment in diaphragmatic excursion indicates that the lesion affects the peripheral portion of the muscle the only part which is pain sensitive. In diseases associated with emphysema the low position of the diaphragm and its reduced excursion as well as the hyperillumination of the lower lung fields are best appreciated on fluoroscopy.

Figure 79 Demonstration of shrunken bronchiectatic lingula. A (Upper) Haziness over left lower lung field blunting of costophrenic sinus. B and C (Lower left and right) Bronchogram reveals dilatation of inferior bronchus of lingula. (Female aged forty five years had emphysema in childhood treated with thoracotomy and drainage course punctuated by occasional hemoptysis and recurring mild respiratory infections.)



Figure 80 Demonstration of pulmonary tuberculosis with cavitation left upper lobe A (Left) PA projection shows a faint annular shadow in left upper lobe partly obscured by overlying ribs B (Right) Lordotic view shows the lesion as a clear cut cavity with a fluid level

ROENTGENOGRAPHY

Projection Techniques

In the following pages the more important projection penetration and contrast techniques will be briefly defined. No attempt will be made to enter into details because this is not the purpose of this book.

Postero Anterior Projection This is the conventional position taken by persons in mass x-ray surveys as well as in the routine chest examination. The patient faces the cassette; the tube stand is approximately six feet to the rear. The patient is directed to take a breath and to hold it while the exposure is made. There are occasions when an additional chest x-ray exposure is indicated in the expiratory phase of respiration. The latter serves to demonstrate small pneumothoraces, localized areas of obstructive emphysema, paralysis of the diaphragm and herniation of one or another of the weak spots of the mediastinum. The amplitude of excursion of the diaphragm and the degree of illuminosity of the lower lung fields in the inspiration and expiration films provide a rough index of respiratory function.

Antero Posterior Projection This position may be more accommodating to obese individuals with protuberant abdomens, also to women late in pregnancy. Apprehensive youngsters are often photographed better by facing the camera.

Lordosis Projection The lordotic position allows better visualization of the apical regions of the lungs by dissociating the clavicles from the upper aperture of the thorax (Figure 80). Right middle lobe disease is also brought out better in this projection because the lobe and fissures are brought tangentially to the central ray.

Lateral Projections This position reveals the interlobar fissures and parts of the lung which are poorly seen in the postero anterior projection. This applies especially to the right middle lobe to the paravertebral retrocardiac and costophrenic sinuses. The contents of the mediastinum and the contour of the diaphragm are also best visualized in this projection.

Oblique Projections Oblique views in the anterior or posterior positions are helpful in visualizing lower lobe disease (Figure 81). When the bronchi are filled with radiopaque substance the right and left anterior oblique projections allow delineation of the tracheobronchial tree at

one sitting. But the preferable way of demonstrating bronchiectasis, especially if the possibility of surgical treatment is under consideration, is to have each lung examined separately in the posterior anterior, lateral and oblique projections.

Several additional projection techniques are available for specific purposes. Chest x rays may be obtained with the patient lying on the back or side or in the Trendelenburg position by tilting the table so that the patient's head is at a lower level.

Penetration Techniques Body Section Roentgenography

The Potter-Bucky diaphragm technique is used in chest x ray examinations if rib involvement is suspected or if a thickened pleura or a thoracoplastic operation prevent visualization of underlying structures (Figure 87). A widely

used technique is sectional roentgenography (tomography, planigraphy, laminography). By this means one is able to study serial sections of a lung with a minimum of interference of overlying structures. The principle underlying sectional roentgenography is as follows: the focal point of the tube moves in one direction as the film moves simultaneously in the opposite; only the part of the chest under examination remains constant. The result is a well defined central area surrounded by blurred shadows outside the plane. The lungs may be sectioned in the lateral as well as in the horizontal planes. Sectional roentgenography finds important uses in delineating cavities or solid masses, major tracheobronchial obstructions and cystic spaces in the lungs or pleura. The procedure is especially useful in the examination of patients immediately prior to resectional surgery as well as after thoracoplastic operations.



Figure 81. Demonstration of bronchogenic cyst. A (Left) PA projection shows suggestion of rounded density at the right border of the heart. B (Right) Right anterior oblique projection reveals the density to be a large, well circumscribed mass. (At operation a bronchogenic cyst was found which was removed.)



Figure 81 Demonstration of cyst. A (Left) No significant abnormalities present in chest. B (Right) Bucky shows ovoid density in lowermost portion of lung, adjacent to spine. (At operation a multiloculated bronchogenic cyst was found attached to left lower lobe, and to fundus of stomach through a small defect in posterior aspect of diaphragm removed successfully.)

Contrast Techniques

Diagnostic Pneumothorax and Pneumoperitoneum The introduction of air into the pleural cavity provides a contrast medium which helps to offset any existing pleural or pulmonary density. By separating the two layers of the pleura with air, one may determine if the disease is within the collapsed lung or in the pleura (Figure 83). If a pleural effusion is present, the fluid is aspirated and replaced by air. Chest x-rays are then taken in various projections, including lateral recumbent positions. With increasing use of exploratory thoracotomy, the indications for diagnostic pneumothorax are becoming fewer. The introduction of air into the peritoneal cavity permits the visualization of structures in the immediate vicinity of the diaphragm. The procedure is occasionally indicated in the differential diagnosis of diaphragmatic hernia, eventration or phrenic nerve paralysis. In the presence of ascites, the replacement of aspirated fluid by air is particularly helpful and practically devoid of

danger. The procedure permits visualization of the liver, spleen and other organs and, occasionally, the demonstration of metastatic deposits in the peritoneal cavity.

Barium Meal This procedure is indicated in the diagnosis of lesions of the mediastinum and lower thoracic cavity which may be associated with or confused with lesions of the esophagus, stomach and the portions of the intestinal tract immediately beneath the diaphragm. A barium meal is helpful in delineating obscure retrocardiac shadows, including esophageal diverticula, cardiospasm and diaphragmatic hernia (Figure 47).

Bronchography The instillation of a radiopaque medium into the bronchi is indicated in suspected bronchiectasis since a definitive diagnosis of this disease cannot be made on the basis of the clinical findings or routine chest x-rays alone (Figures 84 and 85). Bronchography is also of value in marking out distorted or kinked bronchi, bronchocavitary junctions, communications between bronchi and air cysts. Instillation

of iodized oil helps to localize communications between bronchi, pleura and skin. Until recently iodized oil was the medium generally used but, because of certain disadvantages with this agent, chiefly the retention of the iodized oil in alveoli for considerable lengths of time, an aqueous medium is now being employed with increasing frequency. It is beyond the scope of this discussion to dilate on the indications, contraindications, technique and other aspects of bronchography.

Angiocardiography By rapidly instilling into an arm vein 25 to 35 cc. of a 70 per cent solution

of diodrast, and by taking chest x-rays in rapid succession, the large blood vessels and chambers of the heart are visualized (Figure 65D). The technique of angiocardiology, perfected by Robb and Stenberg, has met with universal acceptance in the study of cardiac dynamics as well as in diagnosis of diseases of the chest. Angiocardiography is useful in delineating mediastinal lesions, abnormalities of the superior vena cava especially vena caval obstruction, also arterio-venous aneurysms of the lungs, fibrothorax and other diseases.

Bibliography

DIAGNOSIS

- ADLER H. The Roentgen Localization of the Broncho-pulmonary Segments by Means of Laminography. Particularly in Lung Tuberculosis. *Am J Roentgenol* 70: 218, 1953.
- ADLER R. H., MANTY F. E., JR. and WARP P. F. The Middle Lobe Syndrome and its Relationship to Certain Aspects of Middle Lobe Disease. *J Thoracic Surg* 29: 283, 1955.
- BERGSTROM W. H., COOK C. D., SCANNELL J. and BEREN-

- BERG, W. Situs Inversus, Bronchiectasis and Sinusitis. *Pediatrics* 6: 573, 1950.
- BLADES H. Relative Frequency and Site of Predilection of Intrathoracic Tumors. *Am J Surg*, 54: 139, 1941.
- BOYCE L. A. Cleft Left Upper Lobes and the Split Anterior Bronchus. *Surgery*, 26: 167, 1949.
- BROCK R. C. Post-Tuberculous Bronchostenosis and Bronchiectasis of the Middle Lobe. *Thorax* 5: 1950.
- BROCK R. C. *The Anatomy of the Bronchial Tree*. London: New York & Toronto: Oxford University Press, 1946.



Figure 81. Diagnostic pneumoperitoneum. A (Left) Right to left diaphragm inversion. B (Right) Displaced upward heart slightly. C (Left) Right to left diaphragm inversion. D (Right) Displaced upward heart slightly. In all cases the right leaf of the diaphragm is smooth and regular.



Figure 84 A (Left) Bronchogram showing saccular (cystic) dilations of bronchi of right upper lobe B (Right) Lateral projection shows "saucer-shaped" puddling of iodized oil in affected bronchi, remaining bronchi appear uninvolved (From Rubin, Goldstone and Rubin *Med Clin North America*, 33 391, 1949)

- COHEN, A. G., and GEFEN, A. Roentgenographic Methods in Pulmonary Disease *Am J Med* 10 375, 1951
- CONWAY D. J. A New Medium for Bronchography *Brit J Radiol*, 25 229, 573, 1952
- EFILER D. B. Mediastinal Tumors *Cleveland Clin Quart*, 16 98, 1949
- EWALD, W. BALLON, H. C., and GRAHAM, C. A. Superior Vena Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression *J Thoracic Surg*, 3 352 1934
- ELLIS, F. H., JR., and BRUVER, A. The Roentgenographic Image of the Azygos Vein A Possible Source of Diagnostic Confusion *Proc Staff Meet, Mayo Clin*, 29 508, 1954
- FALLERS, C. J. Cervical Hernias of the Lungs *J Pediatr*, 46 332, 1955
- FELSON, B. Fluoroscopy of the Chest *Dis Chest*, 27 323, 1955
- FORGAN MORF, K. D. and ROBERTSON, P. W. Bronchography with Dionosil *Lancet*, 2 169, 1954
- FRIEDMAN, E. L. Intrapulmonary Pleural Effusions *Am J Roentgenol*, 71 613, 1954
- HAMPTON, A. O., and KING, D. S. The Middle Lobe of the Right Lung Its Roentgen Appearance in Health and Disease *Am J Roentgenol*, 35 721, 1936
- HINSHAW, D. H. Obstructions of the Superior Vena Cava *Am Heart J*, 37 958, 1949
- INGRAM, M. D. HUDSON, G. W., and DAVIS, T. J. Aplasia of the Lung *Am J Roentgenol*, 64 409, 1950
- JACKSON, C. L., and HUBER, J. F. Correlated Applied Anatomy of the Bronchial Tree and Lungs with a System of Nomenclature *Dis Chest*, 9 319, 1943
- KARTIGENER, M. Zur Pathogenese der Bronchiektasen Bronchiektasen bei Situs viscerum inversus *Betr klin Tuberk*, 83 469, 1933
- KATZ, S., HESSEY, H. H., and VEAL, J. R. Phlebography for the Study of Obstruction of the Veins of the Superior Vena Caval System *Am J Med Sci*, 214 7, 1947
- KRAMER, R., and GLASS, A. The Bronchoscopic Localization of Lung Abscess *Ann Otol, Rhin & Laryng* 41 1210 1932
- LACHMAN, E. The Dynamic Concept of Thoracic Topography A Critical Review of Present Day Teaching of Visceral Anatomy *Am J Roentgenol*, 56 419, 1946
- LEWEL, T. F., and HOPKINS, W. A. Roentgenographic Findings in Lesions of the Lingula *Radiology*, 57 193, 1951
- LOVE, J. G. The Scalenus Anticus Syndrome with and without Cervical Rib *Proc Staff Meet, Mayo Clin*, 29 65, 1945
- VILLER, W. S. *The Lung* Springfield, Illinois Charles C. Thomas Publisher, 1937
- NELSON, H. P. The Tracheo bronchial Lymphatic Glands *J Anat*, 66 228, 1932
- ØDEGAARD, H. The Roentgenological Picture in Chronic, Non specific Fibrosis of the Middle Lobe with Special

- Regard to the Value of Plinigraphy *Acta radiol.*, 37 17, 1952
- OLSEN A M Bronchiectasis and Destructive Observations on the Aetiology of Bronchiectasis *Am Rev Tuberc.*, 47 435, 1943
- POPPER, J L, KENDRICK J F., and SMITH W F *Surg Clin North America*, 30 843 1950
- PRYCE, D M, SELLORS, T H., and BLAIR L G Intralobar Sequestration of Lung Associated with an Abnormal Pulmonary Artery *Brit J Surg.*, 35 18 1947
- RICHMAN S., and BURR, W F, JR Localized Bulge of the Right Diaphragm Simulating Neoplasm *Am J Roentgenol* 72 27 1954
- RIGLER L G., and DRICASEN L G The Inferior Accessory Lobe of the Lung *Am J Roentgenol.*, 29 384 1933
- ROSS, G P., and STEINBERG I Practical Method of Visualization of Chambers of the Heart Pulmonary Circulation and Great Vessels in Man *J Clin Investigation* 17 507 1938
- ROBBINS, L I., and HALL, C H The Roentgen Appearance of Lobar and Segmental Collapse of the Lung *Radiology* 44 471 543 1945 41 23 120 760 347 1945
- ROBERTS D J JR DOTTER C T and STEINBERG I Superior Vena Cava and Innominate Veins *Am J Roentgenol* 66 341 1951
- ROGERS J A JR and LEUNG T F Differential Diagnosis of Right Cardiophrenic Angle Masses *Radiology* 61 871 1953
- RLBIN E H., and RLBIN M The Shrunken Right Middle Lobe With Reference to the So Called Middle Lobe Syndrome *Dis Chest*, 18 12 1950
- RLBIN, M and MISHKIN E The Relationship Between Mediastinal Lipomas and the Thymus *J Thoracic Surg* 27 494 1954
- STORCH, C B *Fundamentals of Clinical Fluoroscopy* New York Grune and Stratton 1951
- TINNEY W E and OLSEN A M The Significance of Fluid in the Pleural Space A Study of 274 Cases *J Thoracic Surg* 14 348 1945
- TRULLOW S C., and LUNDEN K Diagnostic Pneumopentoneum *Brit M J*, 2 585, 1935
- WYMAN S M and CYLER, W R Anomalous Pulmonary Artery From the Aorta Associated with Intrapulmonary Cysts (Intralobar Sequestration of Lung) *Radiology* 39 658 1952



Figure 85 Segmental bronchiectasis A (left) Irregular soft infiltrations in left lower lung field B and C (Center and right) Bronchogram in PA and left lateral projections show sacular and cylindric dilations of bronchi in lingula and in superior segment of left lower lobe (Disease discovered after hemoptysis late in pregnancy)



Figure 84 A (Left) Bronchogram showing sacculated (cystic) dilatations of bronchi of right upper lobe B (Right) Lateral projection shows "saucer-shaped" puddling of iodized oil in affected bronchi, remaining bronchi appear uninvolved (From Rubin, Goldsone and Rubin *Med Clin North America*, 33 391, 1949)

- COHEN, A. G., and GRIFFIN, A. Roentgenographic Methods in Pulmonary Disease *Am J Med*, 10 375, 1951
- CONWAY, D. J. A New Medium for Bronchography *Brit J Radiol*, 25 229 573, 1952
- EFFLER, D. H. Mediastinal Tumors *Cleveland Clin Quart*, 16 98, 1949
- EHRICH, W., BALLON, H. C., and GRAHAM, E. A. Superior Vena Caval Obstruction with a Consideration of the Possible Relief of Symptoms by Mediastinal Decompression *J Thoracic Surg*, 3 352 1934
- ELLIS, F. H., JR., and BRAUER, A. The Roentgenographic Image of the Azygos Vein—A Possible Source of Diagnostic Confusion *Proc Staff Meet, Mayo Clin*, 29 508 1954
- FALLIER, C. J. Cervical Hernias of the Lungs *J Pediatr*, 46 332 1955
- FELSON, B. Fluoroscopy of the Chest *Dis Chest*, 27 323, 1955
- FORGAN MORLE, K. D., and ROBERTSON, P. W. Bronchography with Dionosil *Lancet*, 2 369, 1954
- FRIEDMAN, E. L. Intrapulmonary Pleural Effusions *Am J Roentgenol*, 71 613, 1954
- HAMPTON, A. O., and KING, D. S. The Middle Lobe of the Right Lung—Its Roentgen Appearance in Health and Disease *Am J Roentgenol*, 35 721, 1936
- HINSHAW, D. H. Obstructions of the Superior Vena Cava *Am Heart J*, 37 958, 1949
- INGRAM, M. D., HUDSON, G. W., and DAVIS, T. J. Aplasia of the Lung *Am J Roentgenol*, 64 409, 1950
- JACKSON, C. L., and HUBER, J. F. Correlated Applied Anatomy of the Bronchial Tree and Lungs with a System of Nomenclature *Dis Chest*, 9 319, 1943
- KARTAGENER, M. Zur Pathogenese der Bronchiektasen *Bronchiektasen bei Situs viscerum inversus* *Beur klin Tuberk*, 83 489, 1933
- KATZ, S., HUSSEY, H. H., and VEAL, J. R. Phlebography for the Study of Obstruction of the Veins of the Superior Vena Caval System *Am J Med Sci*, 214 7, 1947
- KRAMER, R., and GLASS, A. The Bronchoscopic Localization of Lung Abscess *Ann Otol, Rhin & Laryng*, 41 1210 1932
- LACHMAN, E. The Dynamic Concept of Thoracic Topography—A Critical Review of Present Day Teaching of Visceral Anatomy *Am J Roentgenol*, 56 419, 1946
- LEIGH, T. F., and HOPKINS, W. A. Roentgenographic Findings in Lesions of the Lingula *Radiology*, 57 193, 1951
- LOVE, J. G. The Scalene Anticus Syndrome with and without Cervical Rib *Proc Staff Meet, Mayo Clin*, 20 65, 1945
- MILLER, W. S. *The Lung* Springfield, Illinois: Charles C. Thomas, Publisher, 1937.
- NELSON, H. P. The Tracheo-bronchial Lymphatic Glands. *J Anat*, 66 228, 1932
- ØDEGAARD, H. The Roentgenological Picture in Chronic, Non-specific Fibrosis of the Middle Lobe with Special

- Regard to the Value of Plimigraphy *Acta radiol.*, 37:17 1952
- OLSEN, A. M. Bronchiectasis and Dextrocardia: Observations on the Aetiology of Bronchiectasis *Acta Res Tuberc.*, 47:435 1943
- POPPE, J. L., KENDRICK, J. F., and SMITH, W. F. *Surg Clin North America* 30:843 1950
- PRICE, D. M., SELLOWS, T. H., and BLAIR, L. G. Intralobar Sequestration of Lung Associated with an Abnormal Pulmonary Artery *Brit J Surg.*, 35:18 1947
- RICHTMAN, S., and BARRY, W. F., Jr. Localized Bulge of the Right Diaphragm Simulating Neoplasm *Am J Roentgenol.*, 22:77 1954
- RIGLER, L. G., and ENKESSEN, L. G. The Inferior Accessory Lobe of the Lung *Am J Roentgenol.*, 29:384 1933
- RONA, G. P., and STEINBERG, I. Practical Method of Visualization of Chambers of the Heart Pulmonary Circulation and Great Vessels in Man *J Clin Investigation* 17:507 1938
- ROBBINS, L. I., and HALE, C. H. The Roentgen Appearance of Lobar and Segmental Collapse of the Lung *Radiology* 44:471-543 1945 45:23-170 260 347 1945
- ROBERTS, D. J., JR., DOTY, C. T. and STEINBERG, I. Superior Vena Cava and Innominate Veins *Am J Roentgenol* 66:341 1951
- ROZAS, J. V. JR. and LEIGH, T. F. Differential Diagnosis of Right Cardophrenic Angle Masses *Radiology* 61:871 1953
- RUBIN, E. H., and RUBIN, M. The Shrunken Right Middle Lobe With Reference to the So Called Middle Lobe Syndrome *Dis Chest*, 18:127 1950
- RUBIN, M. and MISHKIN, S. The Relationship Between Mediastinal Lipomas and the Thymus *J Thoracic Surg* 27:494 1954
- STORCH, C. B. *Fundamentals of Clinical Fluoroscopy* New York Grune and Stratton 1951
- TINNEY, W. H. and OLSEN, A. M. The Significance of Fluid in the Pleural Space: A Study of 24 Cases *J Thoracic Surg* 14:248 1943
- TRULFOFF, S. C. and LUNSDEN, H. Diagnostic Pneumoperitoneum *Brit Med J*, 2:585 1955
- WYMAN, S. M. and CYLER, W. H. Anomalous Pulmonary Artery From the Aorta Associated with Intrapulmonary Cysts (Intralobar Sequestration of Lung) *Radiology* 59:658 1952



Figure 85 Segmental bronchiectasis. A (Left) Irregular soft infiltrations in left lower lung field. B and C (Center and right) Bronchogram in PA and left lateral projections show saccular and cylindrical dilations of bronchi in lingula and in superior segment of left lower lobe. (Disease discovered after hemoptysis late in pregnancy.)

Pitfalls in Roentgen Diagnosis

Introduction

THE "NORMAL" chest x ray reveals lung markings which fall within a range of configurations such as may be encountered in persons of the same age, sex, etc. In the individual case however what may appear as an innocuous looking lesion in one may connote serious disease in another. A lesion in the apex of a lung of an elderly white person is apt to be considered of minor signifi-

cance. A similar lesion in a young Puerto Rican is more likely to represent active or potentially active pulmonary tuberculosis. What may appear as increased bronchovascular markings in one may indicate in another an early stage of silicosis or chronic passive congestion or sarcoidosis or sclerodermatous changes depending on the occupation history, clinical and laboratory findings.

The "Normal" Chest

The normal chest allows for considerable deviation from the norm before it falls within the realm of distinctly abnormal depending on many factors technical as well as non technical. A chest exposure taken of a crying child or of a person who does not take a full breath may have the earmarks of an abnormal chest x ray unless one is aware of the conditions under which the exposure was made. Although the borderline between the normal and abnormal is not wide from a roentgenological standpoint it becomes increasingly so as more facts are known of the person—sex, occupation, physical examination history, and laboratory findings and especially if one has some idea of what one is looking for.

The physician who looks at a film for what ever it may reveal may see little, one interested in specific disease or detail as suggested by the history and symptoms, may see a great deal. The film is then no longer a composite of whites and blacks but a delicate portrait possessing many fine shadings. Undoubtedly there is a considerable element of error if one attempts to see more than what meets the eye. But the fact that the experienced radiologist is constantly asking for fuller briefing on the clinical findings proves that

when a physician with a background of information of a particular case looks *into* a film the picture is apt to be most revealing. In other words, a chest x ray preferably serial x rays are much more informative if one suspects the presence of a certain disease than if one is simply on a fishing expedition. This is the reason why mass chest x ray surveys can only serve as a means of screening large numbers of persons with the view of detecting lesions which after further studies may or may not turn out to be clinically significant.

The recognition of an abnormal chest x ray involves a complex mental process which with experience is reduced to a simple routine. One notes immediately whether the disease affects primarily the thoracic cage or the soft structures including the heart and major blood vessels, mediastinum, pleural cavity or lungs. If chiefly in the lungs one notes whether the changes appear to involve primarily the alveolar portions or the vascular system. Although in many cases a clear cut differentiation of the various components entering to the pathologic process can not be made a basic pattern is often apparent. One takes into consideration the size, location

configuration, manner of dispersion and the qualitative characteristics of the infiltrations. One side of the chest is compared with the other. In the presence of unilateral disease, one notes the position of the mediastinum and trachea, the heart, the diaphragm, in fact, all visible structures. The previous chapter dealt at greater

length with this phase of the subject. For the moment, we are concerned chiefly with the limitations of the chest x-ray and the sources of pseudopathological shadows. Obviously an appreciation of the sources of error of chest roentgenography is a prerequisite for a proper evaluation of its reliability.

Pitfalls in Diagnosis

The accuracy of chest roentgenography is determined by a number of variables: those due to (1) failure of the chest x-ray to register disease, 'intrinsic errors', (2) discrepancies in film interpretation on the part of examiners which may give rise to 'subjective errors', and (3) failure of the chest x-ray to record details with sufficient clarity or the presence of artefacts in the film which may be mistakenly ascribed to pathological changes, leading to 'inherent errors' in diagnosis.

INTRINSIC ERRORS

One or more of several factors may be responsible for the obtaining of a normal chest x-ray in the presence of disease, with due regard to the many components which enter into the so-called 'normal chest'. These are (1) the *time* it takes for certain disease processes to evolve to a state where they are discernible roentgenologically, (2) the *size, number* and, possibly, *degree of opacity* which disease processes must attain before they can register roentgenologically, and (3) the *site* of the disease.

Latent Period in Roentgen Diagnosis

There are conditions affecting the lungs and appendages which cause roentgenographic changes almost immediately or within a few hours, if chest x-rays are taken with sufficient frequency. The conditions include acute pulmonary edema, acute bacterial pneumonia, massive atelectasis, as well as chest injuries. The roentgenographic changes may precede symptoms and signs, as a rule, they follow the roentgenographic changes in rapid order. Time in such instances, is usually not a decisive factor in diagnosis insofar as roentgenography is concerned. On the other hand there are diseases which may require days, weeks and even months to make their roentgeno-

graphic appearance, an interval termed by Brailsford, the latent negative radiographic period. In view of the fact that symptoms and signs in many such diseases are often lacking especially in the initial stages, the delay in the appearance of abnormal changes in the chest x-ray is a serious handicap.

Rigler and Exner found that between the time of occurrence of the primary tuberculosis infection and the appearance of roentgenographic changes, a minimum latent period of from three to six months elapses. The particular study was made on nurses in training in whom it was possible to determine the time of infection by noting the change in skin sensitivity from tuberculin negative to positive. In a similar study, but utilizing comparative chest x-rays alone, Louria found the average time between 'negative' and 'positive' films to be five months. Obviously, the interval depends on whether or not one is dealing with a primary infection, which holds true for many student nurses, or reinfection tuberculosis. The latter takes less time to evolve because the element of hypersensitivity, the Koch phenomenon, comes into play. Furthermore, much depends on the frequency and intensity of infection. In any event, a variable period of latency occurs between infection and disease in tuberculosis during which interval the chest x-ray may fail to reveal abnormal changes. In suspected tuberculosis the factor of latency must therefore be taken into consideration in evaluating negative films, especially in dealing with nurses, physicians, hospital personnel and others who may be heavily exposed to tubercle bacilli. The vexing problem of tuberculosis developing in members of the Armed Forces shortly after induction, during the recent World War, in spite of negative preinduction chest x-rays, was due in many in-

stances to failure to take into consideration the factor of latency in the evolution of the disease

Number and Size of Infiltrations

In the normal chest x ray of a young person only the large blood vessels chiefly the pulmonary artery and its major divisions are visible. The vascular markings give the lungs a web like appearance. With age there is a variable degree of peribronchial and perivascular accentuation of markings. The stringy striations are due to prominence of the accompanying lymphatics as a result of chronic irritation and low grade infections. The smallest unit of the lung the primary lobule consisting of terminal bronchiole air ducts alveoli and supplying blood and lymph vessels do not cast shadows unless they are diseased.

William Snow Miller estimated that from 50 to 750 anatomic units are present in a secondary lobule the latter measuring from 1.5 to 2.5 cm in diameter. Since in the usual instance of inflammation reaction it is necessary to have involvement of one or more secondary lobules for roentgenographic portrayal it is evident that disease of appreciable size has to be present before it can be visualized grossly. This feature is exemplified in the evolution of miliary tubercles. Although the lungs possess a dual blood supply and are ideally placed to mirror a hematogenous dissemination of foci the chest x ray may fail to reveal miliary deposits. Roentgenographic evidence of miliary tuberculosis is encountered in only one third of patients whose lungs reveal tubercles at autopsy. Of course in many instances such tubercles represent terminal seedlings. It is well to point out that generalized miliary tuberculosis is not necessarily a disease of infancy and childhood. The disease may occur at any age and is not at all infrequent in individuals of advanced years.

One of the major reasons why the lungs may fail to disclose in the chest x ray the characteristic symmetric dispersion of tubercles in miliary tuberculosis is because the foci have to reach a certain size and number before they are visible in the roentgenogram. Emery and Lorber found chest x rays positive within two weeks of

death if the majority of the tubercles were over 1 mm in diameter and their number 5 to 20 per cm. In the roentgenologically negative group the tubercles were mostly under 0.5 mm wide and their numbers ranged from 1 to 6 per cm.² These investigators found no direct relationship between the histological structure of the tubercle and its roentgenological portrayal. Most observers hold similar views although it would seem offhand that the harder the tubercle (one containing a predominance of fibroplastic elements and collagen tissue) the more easily it should be discernible especially since calcification increases with maturation of the tubercle. Studies by Bloch indicate that the presence of calcium salts in a tubercle is not a reliable index of its roentgen visibility. He found that lesions containing considerable amounts of calcium may possess a lower roentgen density than noncalcified pulmonary foci.

Metastatic neoplastic deposits may likewise escape roentgenological detection unless the individual foci are of appreciable size and number. Fairly large metastatic lesions may be invisible. A patient with an alveolar cell carcinoma was examined at autopsy at the Bronx Municipal Hospital Center and the lungs revealed fairly large metastatic deposits which did not register in a recently taken chest x ray. On the whole metastatic foci because of their uneven size and distribution are recognized easily and at a fairly early stage of development. Surprisingly, Lee found metastases in the lungs of thirty patients of a total of seventy nine examined at autopsy, in whom chest x rays taken within three weeks of death had failed to disclose the pulmonary deposits.

With the introduction of body section roentgenography and with increasing use of excisional surgery the frequent failure of the routine chest x ray to reveal disease has been forcefully brought to the attention of those engaged in the diagnosis and treatment of pulmonary diseases especially tuberculosis. At best the chest x ray shows only the major focus or an aggregate of small foci. Consolidations of appreciable size may be missed in conventional chest x rays. This applies also to cavities. Examination of surg

really excised tuberculous lung tissue almost invariably shows much more disease than is revealed in chest x-rays taken shortly before operation. What appear to be slight changes may be quite deceptive.

It is well to point out that not all annular rarefactions seen in conventional chest x-rays, or even sectional x-rays, represent cavities in the lung. In a recent comparative study of chest x-rays and excised lobes or lungs done at Seton Hospital to be referred to later, many specimens were found which failed to show cavitation although strongly suspected on the basis of the chest x-ray findings. An irregular group of tuberculous foci accompanied by regional emphysema may simulate intrapulmonary cavities. With the introduction of specific antibacterial agents in the treatment of tuberculosis, it has become necessary to reorient one's thinking regarding roentgenological morphological equivalents. A tuberculous process undergoing healing under the effects of antibacterial treatment and in due time resected, no longer reveals the type of pathological changes one has been accustomed to see at autopsy and upon which roentgen interpretation had been based in previous years.

Site of Disease

The portions of the lungs which offer the most difficulties in roentgen interpretation of disease are the bronchi, the corticopleural layer, the vascular and perivascular tissues. However, the physician's attention is often directed to these possible sites of involvement by symptoms and physical signs. Cough and variable degrees of expectoration, occasionally hemoptysis and wheezing rales, feature bronchial disease. A localized wheeze often accompanies bronchial obstruction. Chest pain and friction rub often accompany pleural disease. In addition there are various diagnostic means available to supplement routine roentgenography.

In the presence of partial bronchial obstruction, a chest x-ray taken in complete expiration may reveal a localized area of hyperillumination due to localized emphysema. Following complete occlusion of the bronchus there is atelectasis of the involved bronchopulmonary segment.

In the presence of infection distal to the bronchial obstruction, and the development of lung abscess, the rapid changes in serial chest x-rays may be quite striking. Sectional roentgenography in frontal, lateral and, at times eccentric planes is a useful aid in diagnosis of pulmonary tuberculosis, bronchiogenic neoplasms and other conditions.

The interior of the main bronchi may be examined bronchoscopically and, at the same time, specimens obtained for bacteriological and cytological studies. Bronchography is a valuable means of visualizing the smaller radicles of the bronchi in suspected bronchial obstruction as well as in bronchiectasis. But one must be on guard in using iodized oil in the presence of a bronchial block lest the oil be retained and incite a foreign body reaction. The current use of a quickly absorbable radiopaque substance in watery solution is superior although slightly more irritant and the contrast not as definitive.

Disease concentrated at the periphery of the lung is rarely diagnosable during life although such involvement occurs during the evolution of a number of conditions notably lymphohematogenous tuberculosis and carcinomatosis. If there is an exudate in the pleural cavity and diffuse reticulation of the lungs, especially along the interlobar fissures, one may suspect associated corticopleural involvement. It might be mentioned at this point that Rigler has shown that in the average adult chest as much as 300 cc. of fluid may be present and be unrecognized in the conventional postero-anterior chest x-ray. Even in the lateral projection this amount of fluid may not be clearly visible. Chest x-rays taken with the patient in the lateral recumbent position will reveal free fluid in amounts as low as 100 cc.

Involvement of the pulmonary blood vessels, with minor degrees of parenchymal disease demonstrable grossly, may manifest itself (1) in alteration of the walls of the blood vessels as in syphilis, arteriosclerosis or septic processes, (2) in vascular engorgement, cardiorenal disease, hyperergic states or as a result of toxic irritation of one type or another, and (3) in obstructive phenomena due to thrombosis or embolism of larger

blood vessels or endarteritic occlusive changes of smaller blood vessels. Sudden occlusion of a main pulmonary artery by embolism without infarction may reveal itself roentgenologically in an increased transparency of the involved lung segment as a result of the disappearance of the normal vascular pattern by ischemia (Westermarck). As a rule, symptoms and signs of anoxia as well as other evidence of cardiopulmonary insufficiency are present to draw the physician's attention to the possible involvement of the pulmonary blood vessels.

Diffuse interstitial fibrosis of the lungs, almost invariably associated with variable degrees of alveolar wall thickening, as well as conditions associated with vascular and perivascular changes characterize a number of systemic diseases. The structural alterations are usually not demonstrable roentgenologically unless pronounced. An associated hyperillumination of the lung parenchyma tends to obscure the fine nodulations in the chest x-ray. A number of systemic diseases previously described, manifest themselves in this type of tissue reaction in the lungs.

SUBJECTIVE ERRORS

Since roentgenography is not an exact science, it is not surprising that discrepancies should arise in the interpretation of chest x-rays not only between readers but also by the same reader on reviewing the same films. In addition to faulty judgment, sources of error lie in fatigue and lack of concentration on the part of the examiner. Statistical studies by Yerushalmy and his co-workers have served to emphasize the important role played by the, so called 'personal equation' of the examiner. There is a large field of inter-individual as well as intra-individual disagreement. These investigators found that, in some instances as much as 20 per cent of the films read 'positive' for tuberculosis by one reader was read 'negative' by another.

Although differences in readers' background and experience may explain in part the variations in roentgenographic interpretations, they do not account for the fact that the same individual may disagree with himself in reviewing the same films. In an example cited by Yerushalmy, the first reading revealed fifty-nine films "posi-

tive' for tuberculosis, on the second reading 7 per cent of these were found 'negative' and an additional 3 per cent "essentially negative." On another occasion the same physician read seventy-eight cases "positive" for tuberculosis of which 29 per cent had been "negative" on the first reading and an additional 29 per cent "essentially negative."

In another investigation, the field of disagreement was even more impressive. The particular study dealt with an evaluation of the role of serial chest x-rays in estimating the progress of disease in patients with pulmonary tuberculosis. From this study it appeared that the radiologists on the panel were more consistent in their interpretation than were the chest specialists. The latter in their intuitive attempt to read into the film were 'more inclined to observe improvement in two films than were the radiologists, while the latter were more likely to diagnose stability in the film pair than were the chest specialists. In other words, not knowing the clinical status of the patient, the radiologist is apt to take a noncommittal attitude in questionable cases, the physician, accustomed to view the film from a clinical standpoint, is inclined to take more liberties in interpretation.

Objectivity on the part of the reader may be carried to an extreme. It is common experience that although no significant changes may be discernible in chest x-rays taken at short intervals, one often finds significant degrees of improvement or deterioration when one reviews a series of chest x-rays taken over an appreciable period especially if one is fortified with knowledge of the clinical course of the disease. In reviewing the progress of a case it is essential to examine the first available chest x-rays as well as the most recent ones.

The studies previously cited by Yerushalmy and his co-workers were undertaken primarily to test the reliability of roentgenographic interpretation in mass chest x-ray surveys. As was mentioned previously, such mass surveys simply serve to orient the examiner as to the need of additional examinations in particular cases. The studies demonstrate the fallacy of considering a chest x-ray self-sufficient. They also serve to emphasize the importance of having at least two

independent readings made in the conduct of mass chest x-ray surveys

Clayson and co workers investigated the relative value of miniature (70 mm) films and large films in the roentgenological diagnosis of pulmonary tuberculosis. They found that "within reader" variability (inconsistency in readings regardless of "truth"), was nearly as great with large films as with small films. "Between reader" variability was, if anything, greater on large films than on small films. Accuracy (agreement with "truth") was better in readings of large films but even on large films readings, loss of genuine cases was considerable. These investigators found that accuracy decreased when attempts at increased precision of diagnosis were made, and was especially low in attempted diagnoses of "activity" of lesions. Similar conclusions were reached by Newell and co workers with respect to qualitative description of disease.

In an attempt to measure the reliability and validity of roentgenographic diagnosis in the field of tuberculosis, in order to arrive at a practical descriptive classification of pulmonary lesions as seen on the roentgenogram Newell, Chamberlain and Rigler restudied the problem from various angles including the extent of the disease, qualitative description of the pathologic process and an estimation of activity. They came to the conclusion that a classification of possible tuberculous pulmonary lesions, on the basis of roentgenographic appearances, is not very reliable. They found little to choose among three approaches to the problem: (a) an objective description of the lesion, (b) a quasi-pathologic classification, and (c) a subjective judgment of activity. All were less reliable than the classification of extent of disease in common use (minimal, moderately advanced, far advanced). These investigators concluded that a subjective (intuitive) judgment of activity appeared to be about as reliable as is a description and classification of the objective appearance of the lesion on the film. But in spite of their experience, they still felt convinced that the qualitative appearance of a lesion, as seen on a chest film, must have clinical significance.

In a study of 190 patients with pulmonary tuberculosis who had been treated with resec-

tional surgery at Seton Hospital, Kothari, Shah and I attempted to compare the chest x-ray findings plus whatever information could be obtained from the clinical, bacteriological and bronchoscopic findings and the pathology of the excised specimen. This correlative study was applied with special reference to the presence or absence of cavity and to the presence or absence of tuberculosis of small bronchi. The existence of the latter is often characterized by a triangular distribution of linear markings and contraction of the involved segment or lobe. It might be added, that with respect to the diagnosis of endobronchial tuberculosis, considerable weight was placed on bronchoscopic and bacteriological findings.

The results were quite instructive. In 82 specimens in which "gross" cavitation was found in the specimen, the presence of antrum was suspected in sixty-seven (82 per cent), in 102 specimens in which "gross" cavitation was not found (some had small, blocked cavities and, so called, tuberculomas), cavitation had been suspected clinically in twenty (20 per cent). In other words, in approximately 20 per cent of tuberculous cavities, the diagnosis was incorrect, false positive results being obtained as often as false negative results. A recent study by Mayo and co workers revealed similar results. In ten of eleven lung specimens removed surgically from patients with tuberculosis, areas of translucency were produced by lesions which were filled with solid or liquid caseous material. These areas simulated cavitation or localized emphysema on standard chest x-rays. These investigators suggest that the development of these areas of translucency may result from a physicochemical change in caseous or necrotic tissue, possibly due to a lipid type of degeneration.

In the diagnosis of endobronchial tuberculosis, in which a subjective factor plays a particularly important role, the accuracy of suspicion was approximately the same as that applied to cavitation. In 102 specimens in which significant degrees of tuberculosis were found in the small bronchi, the presence of such involvement was suspected in eighty-three (82 per cent). However, endobronchial tuberculosis was present in nineteen of ninety specimens (21 per cent) in

which the disease had not been suspected clinically. It would seem therefore, that in the interpretation of chest x-rays insofar as it applies to pulmonary tuberculosis, with or without cavitation or endobronchial disease, there is considerable room for error.

INHERENT ERRORS

In addition to the many technical factors involved in the exposure and processing of the x-ray film and which may spell the difference between a readable and an unreadable product, there may be encountered abnormal shadows of increased density caused by artefacts, some easily recognized, others giving rise to misinterpretation. Morgan and co workers also Hefke, have drawn special attention to some of these 'inherent errors'. Artificial shadows may be caused by pins, medals, necklaces, buttons and other opaque substances. Such objects are frequently encountered in chest x-rays taken in mass surveys of persons wearing part of their clothing during the exposure. The experienced reader soon learns to discount these pseudopathological shadows. In hospital practice artificial chest shadows are also often encountered in patients with heavy dressings fixed by adhesive tape. These extraneous shadows are distinguished by the fact that they extend beyond the confines

of the lung fields. Sources of error may be encountered if one fails to have hair braids pinned up or to recognize and make note of obvious chest deformities such as kyphosis, scoliosis, pectus excavatus and other abnormalities.

One has to be on guard against artefacts or pseudopathological shadows because their misinterpretation may be a source of much anguish to the patient and embarrassment to the physician. I have in mind instances of persons who have had routine chest x-rays and who were told to see their physician because of some abnormalities found. The initial chest x-ray may show opacities which depending on their location and the age of the patient, may be suggestive of tuberculosis, neoplasm or some other disease. Retake films may fail to demonstrate these opacities. The original film, when carefully examined may show the 'abnormal' markings to be due either to pressure marks or uneven emulsification of the film or failure to recognize an artefact of one cause or another. But once a person is told that an abnormal shadow is present in the chest x-ray, especially after an examination in a cancer detection or tuberculosis clinic it takes a great deal of persuasion on the part of the physician, often several physicians, before the patient's anxiety is relieved.

Bibliography

DIAGNOSIS

- BIRKELLO C C, CHAMBERLAIN W E, PHELPS D S, SCHOOLS P E, ZACKS D and YERUSHALMI J. Tuberculosis Case Finding: A Comparison of the Effectiveness of Various Roentgenographic and Photofluorographic Methods. *JAMA* 133 359 1947.
- BLOCH R G. Tuberculous Calcification. *Am J Roentgenol* 59 853 1948.
- BRAILS福德 J F. Editorial. The Latent Period which Elapses Between the Onset of a Lesion and the Appearance of Roentgenographic Signs. *Radiology* 46 184 1946.
- BRAILS福德 J F. Factors which Influence the Value of a Radiological Investigation. *Lancet* 1 679 1952.
- CHAPMAN C B and WHORTON C M. Acute Generalized Military Tuberculosis in Adults. A Clinicopathological Study Based on Sixty Three Cases Diagnosed at Autopsy. *New England J Med* 215 239 1946.
- CLAYTON C, FREY H W O, McINTOSH D G, McWINTER, J G, McKINLAY P L and STEIN L. A Preliminary Enquiry Into the Relative Value of Miniature (70mm) Films and Large Films in the Radiological Diagnosis of Pulmonary Tuberculosis. *Brit J Tuberc.* 49 81 1955.
- EMERY J L and LOMBER J. Radiological and Pathological Correlation of Military Tuberculosis of Lungs in Children With Special Reference to Choroidal Tubercles. *Brit M J* 2 703 1950.
- GARLAND L H. On the Reliability of Roentgen Survey Procedures. *Am J Roentgenol* 64 32 1950.
- GRAESER J B, Wu C and ROBERTSON O H. Physical Signs and Roentgenographic Findings in Lobar Pneumonia in Adults. *Arch Int Med* 53 249 1934.
- HEFKE H W. Pseudopathology in Chest Roentgenograms. *Am J Roentgenol* 72 29 1954.
- LEE, I N, et al. quoted by Hugginson. *Am J Surg.* 50 741 1955.
- LODGE T. The Anatomy of the Blood Vessels of the Human Lung as Applied to Chest Radiology. *Brit J Radiol.* 19 77 1946.
- LOUBRI M R. Pulmonary Tuberculosis in Nurses. *New York State J Med.* 41 1573 1941.

Morgan, H. H. 1947

MILLER W. S. *The Lung* Springfield Charles C. Thomas, Publisher 1937

MORGAN, H. H. The Inherent Efficiency of the X-Ray Methods Used in the Detection of Tuberculosis *Publ Health Rep*, 62 701 1947

NEWELL, W. R., CHAMBERLAIN, W. E., and RIGLER L. Descriptive Classification of Pulmonary Shadows A Revelation of Unreliability in the Roentgenographic Diagnosis of Tuberculosis *Am Rev Tuberc* 69 566 1954

RIGLER, L. G. Roentgen Examination of the Chest Its Limitations in the Diagnosis of Disease *JAMA* 147 773 1950

RIGLER L. G. The Possibilities and Limitations of Roentgen Diagnosis *Am J Roentgenol* 61 743 1949

RIGLER L. G., and CYNER F. B. The Latent Period in the Roentgen Diagnosis of Pulmonary Tuberculosis *JAMA* 103 1750 1934

RUBIN C. H., SHAH H. J., and KOTARI J. C. Resectional Treatment of Pulmonary Tuberculosis In preparation

WASSON W. W. The Pathologic Reactions Within the Anatomic Unit of the Lung *Radiology* 30 76 1936

WESTERMARK, N. On the Roentgen Diagnosis of Lung Embolism *Acta radiol* 19 357 1938

VERESHALNY J. The Role of Dual Reading in Mass Radiography *Am Rev Tuberc* 61 443 1950

VERESHALNY J., GARLAND L. H., HARKNESS J. T., HINSHAW H. C., MILLER C. R., SHUPMAN S. J. and ZWERLING, H. B. An Evaluation of the Role of Serial Chest Roentgenograms in Estimating the Progress of Disease in Patients with Pulmonary Tuberculosis *Am Rev Tuberc* 64 725 1951

ZWERLING, H. B., MILLER C. R., HARKNESS J. T., and VERESHALNY J. The Clinical Importance of Lesions Undetected in a Mass Radiographic Survey of the Chest *Am Rev Tuberc*, 64 249 1951

Laboratory and Exploratory Aids

Introduction

THE preceding chapters referred briefly to certain laboratory tests commonly employed in the diagnosis of systemic diseases which may be associated with pulmonary lesions. The following will deal with laboratory diagnosis from the viewpoint of the pulmonary lesions themselves. In the differential diagnosis of such lesions, laboratory tests are utilized to help identify the causative agent, if possible. But, inasmuch as the determination of the cause may be quite difficult, the laboratory is used for a broader survey than might be deemed necessary under ordinary circumstances. At best, the laboratory findings have to be evaluated in the light of the clinical picture as a whole.

In the differential diagnosis of diffuse pulmonary lesions the examination of the sputum, blood, urine and body fluids serves to direct attention to the existence of a generalized disturbance. The results of such tests are seldom conclusive because the laboratory findings vary

at different stages of a disease and the results are more apt to apply to a related group of disorders than to a single one. This feature applies especially to the collagen and hyperergic groups of diseases and, to variable degrees, to most of the conditions described in these pages. To establish the presence of a specific abnormality, one has to depend on the examination of tissues obtained from lymph nodes, skin, bone marrow, liver and other parts of the body. In the absence of demonstrable pathologic changes in the organs and tissues mentioned, it may be necessary to resort to lung biopsy and, occasionally, to exploratory thoracotomy. Even these may not provide the final answer for the reason that pulmonary lesions occurring in a protracted illness, are often transitory phenomena in an undulant disease and the time of appearance of various organ and tissue involvements may have to await further developments.

Examination of the Sputum

BACTERIOLOGICAL FINDINGS

The discovery of a pulmonary lesion in a patient with a systemic disease or, for that matter, under any circumstances calls for a careful bacteriological examination of the sputum for acid fast bacilli and other organisms. Although the sputum findings seldom permit of a specific diagnosis, negative results are of considerable value in ruling out a number of conditions which may closely simulate the type of pulmonary lesions under investigation.

EXAMINATION FOR TUBERCLE BACILLI AND OTHER BACTERIA

The examination of the sputum for tubercle bacilli is of prime importance since pulmonary tuberculosis enters into the differential diagnosis of practically every disease which may affect the lungs and appendages. Until recently, one could subscribe, with few reservations, to the statement that the demonstration of acid fast bacilli in the sputum or gastric washings of a patient with roentgenologically demonstrable pul-

monary disease indicates active pulmonary tuberculosis. With almost equal assurance, one could state that failure to find acid fast bacilli on repeated examinations rules out the presence of active pulmonary tuberculosis. These *ex cathedra* pronouncements are no longer tenable. Under the effects of streptomycin, isoniazid and several of the other antituberculous agents commonly in use today, there is early suppression of growth of the tubercle bacillus. The organisms may be seen in smear but they may fail to grow out in culture and, as a result of loss of virulence, the bacilli may be incapable of infecting susceptible animals. It is now realized that active pulmonary tuberculosis may be associated with negative sputum or gastric washings and inactive tuberculosis, with "positive" sputum containing nonvirulent tubercle bacilli.

A pressing issue, at the moment, are two phenomena which the physician has to be prepared to encounter in pulmonary tuberculosis, either as a newly acquired disease or as a complication of an existing ailment. It is a matter of common knowledge that pulmonary tuberculosis may complicate malignant neoplasms, the lymphomas, especially Hodgkin's disease, bronchial asthma, disseminated lupus erythematosus, sarcoidosis and several of the other diseases described in these pages. What is now generally known is the fact that prolonged use of steroid hormones, currently being employed in the treatment of these conditions, is associated with the added danger of an outbreak of an acute pneumonia nontuberculous as well as tuberculous which may not become immediately apparent because of the masking effect of ACTH and cortisone on infection. Steroid therapy is known to suppress acute inflammation, inhibit repair and increase blood coagulability. These factors favor the development of "silent" pneumonias until they reach explosive stages.

The number of patients developing acute bacterial and fungous infections of the lungs, also caseous and milary tuberculosis, under the effects of steroid therapy, is increasing. In view of this danger, as a precautionary measure, it is advisable to administer 1 Gm streptomycin, once or twice weekly, plus 200 mg isoniazid daily to all pa-

tients under steroid treatment for diseases which are known to be frequent precursors of pulmonary tuberculosis, especially if the lungs reveal what may appear to be inactive foci. By the same token, patients under prolonged steroid treatment for rheumatoid arthritis and other diseases should have frequent chest x-rays to make certain that the lungs do not become the seat of silent infections.

EXAMINATION FOR FUNGI, PARASITES AND OTHER ABNORMAL AGENTS

The systemic diseases which may be associated with diffuse interstitial pulmonary lesions, or with disseminated foci of bronchopneumonia or calcification, often bring to mind the possible presence of a fungous infection. The latter may be a complicating factor as a result of prolonged use of antibiotics or steroid therapy which many patients with pulmonary diseases of the types under consideration are apt to receive. The more common fungous infections which may affect the lungs of human beings are actinomycosis, the blastomycosis, coccidioidomycosis, histoplasmosis, cryptococcosis (torulosis), geotrichosis, nocardiosis and candidiasis (moniliasis), especially the last mentioned.

The simplest laboratory test for the detection of fungi in sputum is direct examination of stained and unstained wet mounts. Schiff's periodic acid stain is a dependable method of demonstrating fungi. Sabouraud's glucose-agar medium, with the addition of antibiotics, is widely used for routine cultures. Special stains and media are utilized for the detection of individual species.

As mentioned, the recognition of the bronchomycoses, especially moniliasis, has become a serious consideration since the introduction of the antibiotics. The elimination of the normal bacterial flora of the mouth and upper air passages, after prolonged use of potent antibiotics, results in an overgrowth of normally nonpathogenic yeasts and fungi, also in disturbances of vitamin metabolism. In a study of moniliasis of the mucous membranes and lungs, as a complication of treatment with antibiotics, corticotropin and cortisone, Bradlund and Holten found that moniliasis developed in eight of 103 patients who had



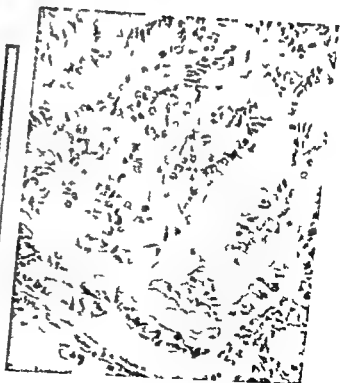
A



B



C



D

(See legend on opposite page)

received corticotropin or cortisone and in seven of 107 patients who had received antibiotics in addition to these hormones. In three additional cases moniliasis was encountered as a complication of antimicrobial treatment alone. In the mild cases the discontinuation of cortisone or corticotropin was not necessary. In the more severe cases the hormones were withdrawn gradually. The treatment of moniliasis consisted of careful attention to nutrition and oral hygiene. Parenteral administration of vitamin B complex also appeared to be of value.

Patients presenting diffuse pulmonary lesions may be found to have parasitic organisms in the sputum. This is true especially of diseases associated with eosinophilia. The life cycles of *Ascaris lumbricoides*, *Strongyloides stercoralis* and *Paragonimus westernmani* involve the lungs either in the larval stages or as mature parasites. Special importance has been ascribed to mites (*Acarina*) in the evolution of bronchopulmonary infections associated with eosinophilia (see Chapter 5).

The sputum may also contain various formed and unformed elements including caseous material and broncholiths, the latter resulting from perforation of bronchi by broken off particles of caseocalcareous lymph nodes. Carbon matter, foreign bodies, food debris, hair from ruptured dermoid cysts and bronchial casts may also be eliminated in the sputum. The sputum should also be examined for fat droplets. Losner and co-workers found lipid material in the sputum of nineteen of twenty patients suspected of having lipid pneumonia and in only two of forty-five patients of a control group. All but two of the patients of the former had previously taken mineral oil or nose drops either continually or at intervals over periods ranging from two to thirty years. These investigators found that the sputum could be considered positive for oil if the Wright stain demonstrated characteristic vacuoles and macrophages and if these vacuoles

stained orange brown with Sudan 4 or if abundant extracellular fat staining material was noted. Although in most instances one is dealing with aspiration lipid pneumonia, occasionally the condition turns out to be an intrinsic form of disease of the type described in Chapter 3.

EXFOLIATIVE CYTOLOGY

In the differential diagnosis of diffuse pulmonary lesions the possibility of a pulmonary neoplasm also comes into consideration. Primary bronchiolar carcinoma or so-called pulmonary adenomatosis as well as metastatic malignancies may be differentiated from nonmalignant systemic diseases with pulmonary lesions. It should be noted that a pulmonary neoplasm may be present coincidentally with a systemic disease and that what may appear to be a systemic disturbance may be caused by a silent malignancy of the lung. The examination of the sputum and bronchial aspirates for exfoliative cytology, i.e. cells shed from surfaces of organs into surrounding fluid is an important step in differential diagnosis of every obscure pulmonary disease.

Considerable advances have been made in recent years in the diagnosis of pulmonary cancer by cytologic examination of sputum and bronchial washings. Improved methods of obtaining fixing and staining smear preparations have contributed largely to the acceptance of the results of exfoliative cytology, not only in the diagnosis of pulmonary neoplasms but also as a screening device in the examination of persons in cancer detection clinics for the possible presence of cancer of the female genital tract, breast and other organs. With respect to the cytological diagnosis of pulmonary malignancies some investigators have found no advantages in the results obtained from bronchial washings as compared to sputum smears.

Malignant changes in sputum or bronchial aspirates are looked for especially in cell nuclei

Figure 86 Exfoliative cytology. A. Circumscribed density in left lower lobe. B. Bronchoscopic washings reveal nests of tumor cells arranged in a pseudoglandular pattern; acini are lined by hyperchromatic low columnar cells of varying size and shape possessing huge atypical and variegated nuclei; cytoplasm of cells is scanty. C. Well circumscribed mass in resected left lower lobe. D. Tumor shows pattern of adenocarcinoma composed of large irregular gland acini with many infoldings and plications; lining cells are similar to those seen in bronchoscopic washings.

with respect to size, hyperchromasia, prominence of nucleoli, irregular mitotic division and other abnormal changes (Figure 86). Nuclear atypia constitutes one of the earliest signs of malignancy. Uninjured cells, occurring in clumps, are apt to be most revealing but even the appearance of single cells may be informative. Experienced pathologists have been able to distinguish specific types of cancer cells but many are loathe to make such distinctions because of the pleomorphic nature of pulmonary malignancies. Foote has been able to differentiate types of cancer cells in as high as 80 per cent of sputum smears and bronchial washings. Paradoxically, this investigator found that sputum smears allowed better recognition of the type of tumor cell than did the bronchial aspirates.

It should be emphasized that atypical cells

highly suggestive of malignancy, may be found in the presence of chronic pulmonary suppuration. It should also be mentioned that metastatic carcinoma of the lungs may likewise give rise to cancer cells in sputum and bronchial washings (Figure 87, cf. Figure 59). False positive cytological diagnoses of cancer vary in the hands of different observers. The average ranges between 2 and 3 per cent but false positive tests have been reported in as high as 10 per cent. In spite of the great advances made in exfoliative cytology, a field to which Papanicolaou has made notable contributions, a definite diagnosis of cancer depends on tissue examination. Although positive cytological findings may offer an added indication for exploratory thoracotomy, the need of resection and the extent of the latter is dictated by the findings at operation.

Examination of the Blood

It is beyond the scope of this book to enter into a detailed discussion of the various blood examinations which may be found helpful in the diagnosis of pulmonary lesions associated with systemic diseases. Suffice it to underline a few tests relating to several of the conditions described. In general, blood examinations seldom supply information as to the exact nature of a disease, excepting those involving primarily or chiefly the hemopoietic system. However, the blood picture may be sufficiently distinctive to apply to a related group of diseases and, what is equally important, repeated blood testing is often of prognostic value.

THE ERYTHROCYTE SEDIMENTATION TEST

The erythrocyte sedimentation test, although nonspecific, is used extensively as an index of activity of disease, especially if the latter is associated with gross inflammation or destruction of tissues. If the cause of the latter is unknown, an accelerated sedimentation velocity of erythrocytes serves to draw attention to the possible presence of a disease which might otherwise escape recognition because of the absence of symptoms or vital signs. If the cause is known, and due allowance is made for any associated anemia, which in itself increases the settling velocity of

erythrocytes, the test possesses prognostic value as an indicator of the course of events and the response to treatment.

It is good practice to inspect the sedimentation tubes the morning after the blood sampling. By this time, the blood has differentiated itself into three distinct layers: plasma, white cells and red cells. The color, appearance, and turbidity of the plasma are often revealing; the former reflects the bilirubin content, the latter, the protein content. The height of the white and red cell layers are roughly proportional to their respective cell volumes. In patients with significant leukocytosis the white cell layer is noticeably deeper as compared to layers in the comparison test tubes. I have come across two cases in which an unusually high column of leukocytes led to further studies and a diagnosis of leukemia.

The erythrocyte sedimentation test is most useful in following the course of prolonged illnesses especially tuberculosis, malignancies and rheumatic fever. The test is also of value in acute and subacute hyperergic, rheumatoid and collagen diseases. The increase of highly labile globulin components of the sera and resulting reversal of the A/G ratio, commonly encountered in these conditions, is associated with rapid blood sedimentation. In fact, the changes in the

serum proteins in the diseases mentioned are the bases of a number of serum and plasma colloid lability tests. The alterations in serum proteins may even cause false positive serologic tests and are believed to be a factor in L E cell formation. False positive Wassermann tests have been found in as high as 16.8 per cent of cases of disseminated lupus erythematosus in 10.6 per cent of cases of polyarteritis nodosa and in 6.6 per cent of cases of rheumatoid arthritis.

DERMATOLOGICAL FINDINGS

Reference was made in Chapter 4 to certain pulmonary diseases notably tuberculosis and malignant neoplasms which may be associated with hemolytic anemia leukenoid reactions leukopenia and other atypical blood findings. Leukocytosis, with a shift to the left is common in rheumatic fever during acute exacerbations of rheumatoid arthritis in polyarteritis nodosa and dermatomyositis. On the other hand disseminated lupus erythematosus is more often associated with leukopenia and thrombocytopenia unless there is superimposed infection in which case variable degrees of leukocytosis may appear. Although an excess of eosinophils in the blood (more than 300 cells per cu mm or more than 5 per cent in the differential count) is a feature of most allergic states the absence of eosinophilia does not rule out allergy. Eosinophilia as shown in Table 9 is encountered in a variety of diseases including dermatologic disorders, parasitic infestations and various infections. An excess of eosinophils is also seen in dermatomyositis and occasionally in eosinophilic granuloma.

THE L E TEST

In the discussion of disseminated lupus erythematosus reference was made to the significance of the finding of L E cells in the peripheral blood and/or bone marrow (Figure 30B). It is becoming increasingly apparent that the L E test is highly specific. Noteworthy is the fact that presumably false positive tests are met with under circumstances which of themselves add importance to the significance of the phenomenon. Of a total of 4200 examinations Lee obtained seventy-two positive L E tests. Sixty

TABLE 9

CAUSES OF EOSINOPHILIA

- 1 Allergic disorders: bronchial asthma, urticaria, angio-neurotic edema, hay fever
 - 2 Skin diseases especially pemphigus and dermatitis herpetiformis
 - 3 Parasitic infestations especially parasites which invade the tissues e.g. trichinosis, elaeococcus disease less regularly in intestinal parasitism
 - 4 Certain infections e.g. scarlet fever, chorea, erythema multiforme
 - 5 Certain diseases of the hemopoietic system: chronic myelocytic leukemia, erythremia, Hodgkin's disease after splenectomy, pernicious anemia
 - 6 Following irradiation
 - 7 Miscellaneous disorders: periarteritis nodosa, tumors of the ovary or those involving serous surfaces of the peritoneum
 - 8 Loeffler's syndrome, tropical eosinophilia
 - 9 As a familial anomaly
- (From Wintrobe: *Clinical Hematology* 3d Ed. Philadelphia: Lea & Febiger 1951)

six of these had demonstrable disseminated lupus erythematosus. In the remaining six there were suggestive but not conclusive indices of the disease. These six included patients who showed one or more features commonly associated with lupus such as rheumatoid arthritis, arthralgias, hemolytic anemia, leukopenia, thrombocytopenia, unexplained facial rashes, false positive serologic test for syphilis and the like. Lee encountered one patient with interstitial pulmonary fibrosis in whom a positive L E test was obtained and only one of proved disseminated lupus erythematosus associated with a negative L E test.

Wers and Swift studied L E preparations in 350 patients. L E cells were found only when lupus erythematosus was the leading or possible diagnosis. In agreement with others, these investigators suspect that disseminated lupus erythematosus is probably a phenomenon of hypersensitivity. There is some evidence that the L E phenomenon depends on an antigen-antibody mechanism found in patients with a high serum globulin, possibly a distinct gamma fraction. Reference was made elsewhere to the reported occurrence of L E cells in association with penicillin reactions, pernicious anemia, dermatitis herpetiformis, multiple myeloma, malaria, tuberculosis and leukemia. Joske and King reported the finding of L E cells in the blood from two patients with active chronic hepatitis, probably of



Figure 87
ings and f
prominent

Figure 88 Section through skin. Subcutaneous tissue shows poorly circumscribed granulomatous lesion with mononuclear and occasional giant cells, consistent with positive Kveim test

viral origin. It should be noted that the L E test may be negative in patients under steroid treatment. Weiss and Swift suggest that all patients with rheumatoid arthritis should have frequent L E tests done, even if they show minimal

symptoms suggestive of lupus erythematosus. For reasons mentioned in Chapter 6, this applies also to patients with diffuse interstitial pulmonary fibrosis.

Skin Tests

In the differential diagnosis of disseminated pulmonary lesions, occurring in the course of systemic diseases, there is occasional need for skin tests. Skin testing is indicated in suspected tuberculosis, sarcoidosis, fungous infections and diseases of hypersensitivity.

TUBERCULIN SKIN TEST

With the marked decrease in the mortality and, to a lesser degree, morbidity from tuberculosis in the past few years, the tuberculin test has assumed greater importance. The extremely

low infection rate of tuberculosis in children has relegated to the background the value of skin testing as a case-finding method since the occasional positive reactor hardly pays for the time and effort involved. *Pari passim*, the use of tuberculin is becoming increasingly valuable as a diagnostic test since a positive test indicates probable recent infection with tuberculosis and points to a possible source of contact at home. Chest x rays of contacts often lead to the discovery of active tuberculosis in a member of the family.

The incidence of false positive reactions to

tuberculin increases as the dose is increased. A significant percentage of reactions following the second strength PPD (purified protein derivative) are nonspecific. A positive skin test after the first dose of PPD is therefore, more informative. On the basis of exhaustive investigations, Edwards and co-workers found that a definite induration of the skin, of 5 mm or more, after inoculation of 0.0001 mg. of standard PPD tuberculin, is specific for infection with tuberculosis. A depression of skin sensitivity to tuberculin may result in false negative reactions during measles, influenza, brucellosis and pregnancy. The lowering of skin sensitivity to tuberculin in these conditions holds true for other skin antigens. In fact, the occurrence of negative tuberculin skin reactions in patients with sarcoidosis is ascribed to a similar immunologic mechanism. It should be mentioned that the use of streptomycin and isoniazid has raised some doubt as to the reliability of tuberculin skin testing when patients are receiving antituberculosis drugs. A marked decrease and even a reversion of tuberculin hypersensitivity has been observed in experimental animals treated with these agents. Recently Robinson and co-workers duplicated this phenomenon in infants with primary tuberculosis.

KVEIM SKIN TEST

This test was originally introduced by Williams and Nickerson in 1935, on the hypothesis that sarcoidosis might be a virus disease. Although a red papule was observed in four patients with suspected sarcoidosis and none in the controls, the nature of the skin reaction was not studied histologically, and the real significance of the test escaped recognition. Six years later Kveim discovered that the skin lesions duplicated histologically those of sarcoidosis. Shortly thereafter the Kveim test became widely accepted as a diagnostic test of sarcoidosis.

The Kveim test consists of an intradermal injection of saline suspension of sarcoid tissue, obtained from a patient with proved, active sarcoidosis. The development of a reddish nodule at the site of injection within approximately two months, which on histological examination re-

veals characteristic sarcoid structures, is indicative of sarcoidosis in the majority of suspects (Figure 88, cf. Figure 39). The site of inoculation has to be observed for at least six months before the test is considered negative. Positive skin tests have been obtained several years after inoculation.

The matter of 'specificity' of the Kveim test is still not entirely settled. Sones and co-workers tested twenty-four patients with sarcoidosis and obtained sarcoidal Kveim reactions in 26.8 per cent of eighty-two tests. In nineteen patients with tuberculosis positive reactions were obtained in sixteen tests. In eighteen control subjects, 14.3 per cent of twenty-eight tests showed a positive sarcoidal reaction. The test was considered positive only if there was an epithelioid cell tubercle eight weeks after the intradermal injection. Clinically positive, but histologically nonspecific tests, revealed either nonspecific granulomatous tissue or chronic, nonspecific inflammation. Sones and his co-workers conclude that the clinical use of the Kveim test as an aid in the diagnosis of sarcoidosis is not justified. These conclusions are at variance with those of the majority of investigators.

The Kveim test is nonspecific since similar, although usually not identical tuberculoid skin responses have been obtained after injections with BCG vaccine, dead as well as virulent tubercle bacilli, normal spleen suspension, leukemic lymph node suspension and foreign bodies (beryllium silica). However, the elicitation of a positive Kveim test confirms the presence of active sarcoidosis. In most cases however the disease can be diagnosed without the long wait necessary for a confirmatory Kveim test. In patients with regressing disease, the group in which one is usually in the greatest need of laboratory aid the Kveim test is often negative. It should be noted that the administration of steroids interferes with the development of the sarcoid nodule.

SKIN TESTS IN FUNGUS DISEASES

As diseases caused by bacteria are being brought under control, fungous infections are assuming increasing importance, not only with respect to incidence but also with respect to

virulence. The more frequent fungus infections which may affect the lungs and cause disseminated lesions of the type encountered in systemic diseases are histoplasmosis, coccidioidomycosis, moniliasis and the blastomycoses. Although the presence of a mycotic infection may be suspected from the place of residence, symptoms and chest x-rays, a definitive diagnosis can seldom be made without confirmatory laboratory findings. These involve the isolation of the fungus, complement fixation and skin tests.

Skin tests are applied in the diagnosis of histoplasmosis, coccidioidomycosis and the blastomycoses. The tests are administered and read in a manner similar to that of the tuberculin test. Smith draws attention to the fact that skin tests in fungus diseases are negative in the initial stages of the infection and often even in advancing disease. In fact, patients may progress to death without the development of positive skin tests. This applies especially to histoplasmosis. Terminal cases of histoplasmosis, coccidioidomycosis and blastomycosis frequently become anergic and give negative skin reactions. A positive skin test in a fungous disease, like the tuberculin test, simply means present or past infection.

Because of the occurrence of a common antigen in coccidioides immitis, *Histoplasma capsulatum* and *Blastomyces dermatitidis*, skin tests may give cross-reactions. For this reason, Smith advocates the simultaneous use of histoplasmin, coccidioidin and blastomycin, irrespective of whether or not a particular mycosis is suspected. The specific reaction is always larger when the three antigens are given simultaneously and no difficulty is encountered in interpretation. It should be mentioned that complement fixation tests for coccidioidomycosis, histoplasmosis and blastomycosis are of greater diagnostic value than skin tests. This is due to the fact that antibodies are not stimulated by subclinical infections and the titer continues to rise with advancing disease. The problem of the isolation of fungi has been referred to earlier in the chapter.

The specific reaction is always larger when the three antigens are given simultaneously and no difficulty is encountered in interpretation. It should be mentioned that complement fixation tests for coccidioidomycosis, histoplasmosis and blastomycosis are of greater diagnostic value than skin tests. This is due to the fact that antibodies are not stimulated by subclinical infections and the titer continues to rise with advancing disease. The problem of the isolation of fungi has been referred to earlier in the chapter.

Chest Aspiration

Serous membrane involvement is a prominent feature of systemic diseases caused by lymphohematogenous infections, hypersensitivity states and metastatic neoplasms. This book contains reference to serosal lesions of the pleura, pericardium, peritoneum and joints, especially to pleural effusions occurring in the course of the conditions mentioned. Occasionally the appearance of a pleurisy heralds the onset or recrudescence of a systemic disease, although symptoms of the latter may not become apparent until months or years later. In some cases the pleurisy is an abortive manifestation of what would ordinarily be a systemic disturbance.

The classical example of the significance of an "idiopathic" pleural effusion is exemplified in tuberculosis. Kallner examined 580 instances of "idiopathic" exudative pleurisy, one to twenty years later. He found that no less than 39 per cent developed manifest tuberculosis. Others have come to similar conclusions. The prognostic implications of "idiopathic" pleurisy should not be lost sight of with respect to other diseases, notably the rheumatoid diseases, disseminated

lupus erythematosus, diseases associated with other hypersensitivity states, malignant lymphomas and various other conditions described in previous chapters.

A diagnostic chest aspiration is indicated in practically every patient found to have a pleural effusion even if the cause appears to be obvious. The examination of the fluid does not necessarily lead to a correct diagnosis. As a rule, an effusion in the young points to tuberculosis, in the elderly, to neoplasm. A diagnosis of tuberculosis is established if acid fast organisms are cultured from the fluid. The testing should be done before antituberculosis treatment is instituted. The diagnosis of neoplasm may be established by the cytological examination of the fluid. In spite of careful laboratory studies, a large proportion of pleural effusions cannot be diagnosed. As indicated, some of these represent pleural manifestations of systemic diseases which may or may not be clinically apparent.

The significance of fluid in the pleural space was studied by Tunney and Olsen. In no less than 170 of 444 cases (38 per cent) a diagnosis

of the underlying disease was not established. Of the 170 undiagnosed, a tentative diagnosis of tuberculosis was made in fifty-eight and of metastatic carcinoma in forty-six. In the remaining sixty-six, even less definite diagnoses were entered. The causes of pleural fluids exclusive of tuberculosis and carcinoma include congestive heart failure, lymphoblastoma, pneumonia, cirrhosis of the liver, chronic nephritis and nephrosis, benign neoplasms of the ovary, fungous diseases, disseminated lupus erythematosus, pulmonary infarction, trauma to the thorax and subdiaphragmatic abscess.

In differentiating transudates from exudates, chief reliance is placed on the protein content

the specific gravity of the fluid and to a lesser extent the presence of formed elements. Pad dock found a linear relationship between the protein content and the specific gravity which was as close as that in the blood. In exudates the protein is generally more than 3 gm. per cent and the specific gravity more than 1.020. The protein content is usually proportional to the degree of inflammation present. It should be noted that bloody effusions, although occurring more often in patients with malignant neoplasm, are not diagnostic of cancer. A high percentage of lymphocytes and a reduction of glucose (less than 60 mg. per cent) are strongly indicative of tuberculosis.

Bronchoscopy

Bronchoscopy is often employed in the diagnosis of obscure bronchopulmonary diseases including disseminated lesions of the type described in these pages. Even if the cause seems obvious, bronchoscopy may be indicated to rule out complicating elements or coexisting disease. Bronchiogenic carcinoma is being encountered with increasing frequency in elderly males with pulmonary tuberculosis. The latter is occasionally superimposed on sarcoidosis, disseminated lupus erythematosus and malignant lymphomas. As mentioned earlier in the chapter, the bronchoscopic examination includes the obtainment of biopsy specimens and washings for exfoliative cytology, bacteria, fungi and foreign particles.

In the diagnosis of disseminated pulmonary lesions commonly occurring in the course of systemic diseases, bronchoscopy is done primarily to rule out carcinoma and tuberculosis, the two conditions which often mimic the former. It would seem, however, that insufficient use is

made of bronchoscopy in its own right as an aid in the diagnosis of systemic diseases with pulmonary lesions. Systemic diseases associated with tracheobronchial lymph node enlargement and there are quite a number of these may show changes in the mucosa and submucosa of adjacent bronchi. Biopsies obtained from the latter may reveal important clues of the identity of the underlying disease. In sarcoidosis, for example, the trachea and bronchi are occasionally involved and in several cases reported by Benedict and Castleman, also Olsen, it was possible to make a diagnosis by bronchoscopic biopsy. In so-called primary amyloidosis of the lungs, the favorite sites of deposition of amyloid are in the trachea and major bronchi (see Chapter 3). Possibly hyperergic states and diffuse vascular diseases may also be reflected in changes in the bronchi. A searching investigation along the lines indicated might prove fruitful.

Needle Biopsy of the Liver

In the diagnosis of disseminated pulmonary lesions occurring in the course of systemic diseases, a needle biopsy of the liver is occasionally helpful. The test was originally introduced as a means of studying hepatic disease but it soon became apparent that tissues obtained by needle puncture of the liver may not only reveal in-

trinsic disease but also lesions associated with systemic disturbances.

In a study of 650 needle biopsies of the liver, Klatzkin and Yesner found granulomatous lesions in patients with sarcoidosis, tuberculosis, erythema nodosum, brucellosis, viral infections, including infectious mononucleosis and in actino-



Figure 89 Needle liver biopsies A Small polygonal cells with poorly defined outlines and finely vesicular eosinophilic cytoplasm nuclei are ovoid hyperchromatic and exhibit occasional mitotic figures (Metastatic anaplastic carcinoma of liver primary in breast) B Small closely packed granuloma made up of epithelioid cells containing giant cells no caseation surrounding zone of thin fibrous bands separating granuloma from liver parenchyma (Sarcoidosis with hepatosplenomegaly)

mycosis These investigators refer to the reported occurrence of miliary hepatic granulomas in early syphilis, leprosy, tularemia, coccidioidomycosis and blastomycosis To these may be added primary and metastatic carcinoma of the liver (Figure 89A), amyloidosis and leukemia The test is applicable to a wide variety of diseases

With respect to systemic diseases, probably the greatest field of application of needle liver biopsy is in sarcoidosis (Figure 89B) This is not surprising in view of the frequency of liver involvement in this disease In 1944, Pinner and I reviewed the published reports of forty-three autopsies on patients with sarcoidosis In no less than seventeen cases lesions were found in the liver Careful studies of the liver would have undoubtedly revealed a much higher incidence of hepatic involvement In twenty cases of histologically proved sarcoidosis Klatzkin and Yesner

were able to demonstrate submiliary granulomas by needle biopsy of the liver in fifteen but in none of the five with a presumptive diagnosis In ten of the former, the histological confirmation of the diagnosis rested on the liver biopsy findings alone Noteworthy was the finding of a striking resemblance in morphology between the hepatic lesions of sarcoidosis and those of tuberculosis, erythema nodosum and brucellosis

Details of technique and the complications of needle biopsy of the liver do not concern us here Some investigators prefer the transthoracic approach in the ninth or tenth intercostal space in mid or anterior axillary line, others, the abdominal route The major complication is hemorrhage, especially if the needling is done in a jaundiced patient It is essential to administer vitamin K to the latter several days before the puncture is done and to have compatible blood

immediately available if needed. Most physicians prefer not to do liver biopsy in such cases unless the latter is absolutely indicated.

The incidence of complications following needling of the liver varies in the hands of different investigators. In a collected series of 1200 liver biopsies, Sherlock found reports of eight deaths. Among the 650 biopsy patients, reported by Klitskin and Yesner, there were a few minor

but no fatal complications. In a report by Morey and co-workers, on 139 needle biopsies of the liver, hemorrhage was encountered in four patients, in one of whom it proved fatal. These authors noted that the incidence of hemorrhage and pain is much less when the puncture is made through the abdomen as compared to the trans-thoracic route.

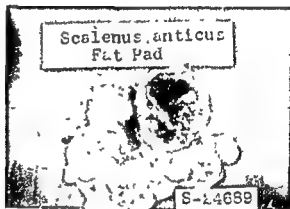
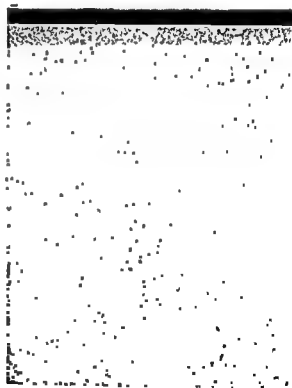


Figure 90 Prescalene lymph node biopsy. A Hilar and right paratracheal lymph node enlargement, irregular, linear strands in subapical regions. B Fat pad with lymph nodes removed from right prescalene space. C Lymph node showing noncaseating sarcoid tubercles.



Prescalene Lymph Node Biopsy

Systemic diseases associated with disseminated pulmonary lesions are often associated with lymph node enlargement. If a peripheral lymph node is available for biopsy, the histological changes are often decisive in the diagnosis. There are many occasions, however, when easily removable lymph nodes are not found and under these circumstances increasing use is being made of prescalene lymph node biopsy, a diagnostic procedure first proposed by Daniels in 1949. The method involves the removal of the lymph nodes or the lymphoid tissue from the fat filled space overlying the sclelus anticus muscle (Figure 90). Lymphatics of the right lung drain into the right paratracheal nodes; these drain also the inferior portion of the left lower lobe via the carinal nodes. Lymphatics of the upper mass of the left upper lobe drain into the left paratracheal nodes. But, lymphatics of the superior segment of the left lower lobe and those of the lingula drain into the left or right paratracheal nodes. For lesions of the left midlung, bilateral exploration is necessary. (Connor)

The results obtained with prescalene lymph node biopsy depend on the nature of the material studied. In a representative group of 187 patients, reported by Shefts and co-workers, abnormal lymph nodes were found in sixty-seven (35.8 per cent). In suspected sarcoidosis the biopsy may give positive results in as high as 66 per cent (Cartensen and co-workers). In car-

cinoma, the incidence of finding metastatic invasion of the cervical lymph nodes is also quite high. In the presence of nondescript pulmonary disease such as unresolved pneumonia, unexplained hydrothorax or isolated pulmonary lesions, the prescalene lymph node biopsy is not often revealing. In forty-one such patients, Caylandall found only eight showing specific lesions in the resected lymph nodes. In addition to sarcoidosis and metastatic malignancies, prescalene lymph node biopsy may give positive results in tuberculosis, malignant lymphomas, histoplasmosis, silicosis and several other conditions.

Harken and co-workers found that of seventy-eight proved cases of carcinoma of the lung, thirty-one (40 per cent) showed metastases to the superior mediastinal or cervical lymph nodes. Harken's operation involves a cervicomediastinal exploration and the use of a laryngoscope as a lighted retractor in order to expose the upper mediastinal lymph nodes, a dissection much more extensive than that involved in Daniel's operation. One half of the positive results in Harken's cases came from tissues removed from the mediastinum and not the scalene fat pad. In his experience with 300 cervicomediastinal explorations, Harken and co-workers encountered no serious complications. Hemorrhage occurred in two patients and pneumothorax in an additional two; the former was controlled with Gelfoam, the latter, with catheter drainage.

Lung Biopsy and Other Surgical Explorations

Scadding lists approximately eighty conditions which may be associated with diffuse nodular or reticular pulmonary lesions (Table 10). On the basis of chest x-rays, history, physical findings and the various laboratory tests described previously, it is possible to arrive at a correct diagnosis in possibly 50 per cent of cases. In the remainder a diagnosis cannot be made with any degree of certainty without the help of exploratory procedures, involving minor or major surgical operations. The most important of the latter is a lung biopsy. But even with the aid of a lung biopsy a diagnosis is not always possible for the

reason that the appearance of the histological specimen may be in keeping with more than one condition.

A practical method of performing a lung biopsy with a minimum degree of danger to the patient, was first described by Khessen and co-workers, in 1949. With minor modifications, this procedure has been adopted and is being used with increasing frequency. The operation is done under general endotracheal anesthesia since the latter facilitates inflation of the lung, when needed and provides a patent airway at all times. A curved, lingular incision, approximately five

TABLE 10
LIST OF CAUSES OF DIFFUSE NODULAR OR RETICULAR
LING SHADOWS

	Chronic	Acute		Chronic	Acute
1 Infections			After haemoptysis		+
Bacterial			Other forms of diffuse focal aspiration pneumonia		+
Tuberculosis	+	+	Keroneche	+	+
miliary	+	+	Island paraffin (lipoid pneumonia) iodized oil	+	+
acino-nodular	+	+			
Streptococcal		+	4 Associated with Cardiovascular Disease		
Fr. cellulæ & bacillus (Staphylococcal)		+	Pulmonary oedema		+
Brucellosis		+	Uræmic lung		+
Tularæmia		+	(Rheumatic pneumonia)		
Mycotic			In mitral stenosis hæmosiderosis miliary	+	
Coccidioidomycosis	+	+	ossification	+	+
Histoplasmosis	+	+	Multiple pulmonary embolism		
Blastomycosis	+	+	Right sided infective endocarditis	+	
Torulosis		+			
Actinomycosis		+	5 Of Uncertain Aetiology		
Others			Sarcoidosis		
Viral			Associated with erythema nodosum		
Unidentified pneumonotropic viruses		+	Diffuse interstitial fibrosis		acute
Variella		+	chronic		
Stevens Johnson syndrome (Paritacosis)		+	Idiopathic pulmonary hæmosiderosis		
Parasitic			6 Associated with General Constitutional Diseases		
Schistosomiasis	+		Honeycomb lungs		
2 Inhalation			Developmental type		
Dusts			Anthraxosis		
Coal-miner's pneumoconiosis	+		Associated with biliary cirrhosis		
Silica	+		Associated with pulmonary borders		
Asbestos	+		Granuloma of unknown aetiology		
Beryllium	+	+	Nevoidermatid dysplasia (cutaneous sclerosis)		
Aluminium	+		Rheumatoid arthritis		
Graphite	+		Scleroderma		
Talc	+		Generalized lupus erythematosus		
China clay	+		Cystic disease of the pancreas		
Iron	+		7 Reticulosis and Blood Diseases		
Barium	+		Leukaemia		
Silver	+		Hodgkin's disease		
Manganese		+	Mycosis fungoides		
Platinum osmium vanadium		+	Lymphosarcoma		
Megacose	+	+	8 Neoplastic		
Cotton		+	Primary bronchial carcinoma		
Mouldy hay grain etc.		+	Metastatic blood borne		
Irritant gases and vapours			lymphangitis carcinomatosa		
Phosgene		+	9 Allergic		
Nitrous fumes	+	+	Eosinophilic infiltrations of the lungs		
Mustard gas, Lewisite		+	Periarteritis nodosa		
Others			Transient infiltrations in asthma		
3 Aspiration			10 Associated with Bronchitis, Emphysema and Bronchiectasis		
Dysphagia pneumonitis	+	+	Diffuse fibrosis		
After coma		+	Cylindrical bronchiectases		
After resuscitation from drowning		+			

(From Scadding *Tubercle*, 33 353 1952)

to six inches in length, is made over the fourth or fifth intercostal space below the breast. The intercostal space selected depends upon the habitus of the individual. The side showing the maximum pathology is chosen. The incision is carried down through the subcutaneous tissues, pectoral and intercostal muscles. To facilitate closure, a row of sutures is placed through the intercostal muscles along the upper and lower

borders of the interspace selected before the pleural cavity is entered, permitting rapid closure and approximation of the ribs.

After the pleural cavity is entered, the pleura is inspected and the lung palpated. Immediately prior to incision of the pleura the anaesthetist is alerted and positive pressure applied and maintained until the muscles are closed. In this way the lung is maintained in an inflated state during

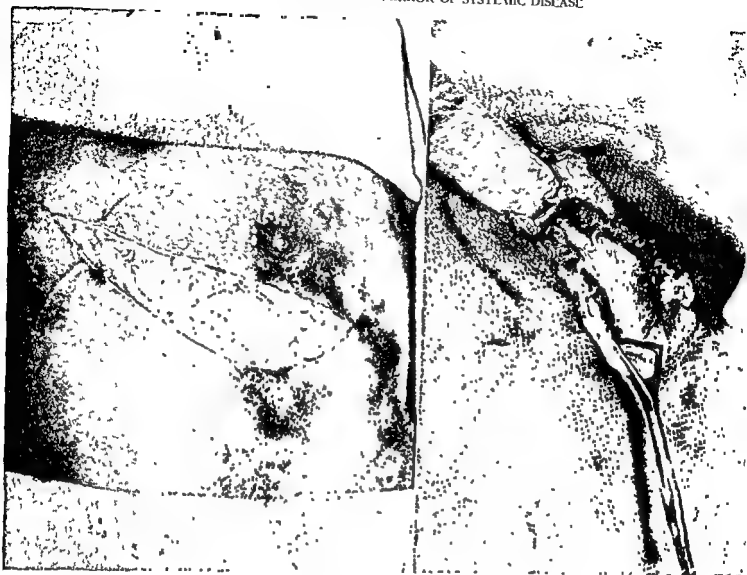


Figure 91 Lung biopsy A Inframammary intercostal incision
B Edge of lung clamped and delivered through incision

the entire procedure thereby minimizing the risk of a large pneumothorax. Depending on the side operated on, the anterior edge of the lower lobe or of the middle lobe on the right side, or of the lingula on the left, is grasped with a lung clamp and delivered through the incision (Figure 91). As a rule, it is not necessary to insert a retractor. The lung segment is doubly clamped and the segment of the lung excised. The raw edge is approximated with a continuous catgut suture proximally and interrupted sutures along the edge. After inspection for bleeding and air-leaks, the lung is permitted to retract into the pleural

cavity and the chest wall is then resutured. It is usually not necessary to apply waterseal drainage after the operation but a chest x-ray should be obtained soon after to determine the amount of pneumothorax, if any. The procedure is well tolerated by patients even with low respiratory reserve.

Table 11 lists the various diagnoses arrived at by three groups of investigators, in a collected series of 197 patients, after the performance of lung biopsies. Approximately one-third of the patients were found to have diffuse, interstitial or idiopathic pneumonitis with or without fibro-

TABLE 11

DIAGNOSIS OF PULMONARY LESIONS ESTABLISHED BY
LUNG BIOPSY IN 197 PATIENTS

Categories	No. of Cases
1 Infections	21
A Tuberculosis	14
B Fungous	6
C Bronchitis	1
2 Neoplasms	33
A Primary	5
B Metastatic	28
3 Inhalational Diseases	49
A Berylliosis	10
B Anthracosis or Silicosis or Combined	15
C Asbestosis	4
4 Sarcoidosis	33
5 Interstitial or Idiopathic	61
Pneumonitis with or without Fibrosis and/or Emphysema	
6 Miscellaneous	70
(Eosinophilosis in association with diseases of hypersensitivity, fibrocystic disease of pancreas, pyoderma, vascular and nonspecific causes)	

Total

197

(Combined results of Effler and co-workers, Theodos and co-workers and Prior and co-workers (see Bibliography))

sis and/or emphysema (Figure 92). As indicated in Chapter 6, there is every reason to believe that continued use of lung biopsies will in time permit the differentiation of a number of agents which may cause diffuse interstitial lesions in the lungs. It stands to reason that excised lung specimens, studied during the early dynamic phases of a disease, are invaluable in diagnosis. The performance of a relatively simple operation, associated with a low morbidity, more than compensates for the greater danger involved in attempting to treat undiagnosed disease.

As shown in Table 11, infections and neoplasms constitute sizable segments of the final diagnoses obtained in lung biopsies. Inhalational diseases also constitute a large group. If one combines the groups revealing sarcoidosis, metastatic neoplasms, variable numbers of diffuse interstitial fibroses and the miscellaneous it is apparent that more than 50 per cent of patients in whom lung biopsies are presently being performed reveal pulmonary lesions which are part of systemic disturbances.

In order to obtain the maximum information

from a lung biopsy, the histological examination of the resected specimen should be supplemented with as many additional examinations as possible. Theodos and co-workers stress the importance of utilizing micromincration and spectro photometry in suspected inhalational disease. Such examinations are of considerable value in forensic medicine. Bacteriological and biochemical examinations of lung biopsy specimens, especially the latter, will in the future undoubtedly add greatly to our understanding of many currently obscure diseases.

When a major lesion is present in the pleura, in a location where it can be readily approached by operation, a pleural biopsy may be indicated. In most instances one is dealing with an inflammatory, granulomatous or neoplastic disease which has provoked a thickly organized pleural membrane and it is difficult to ascertain the nature of the underlying disease. The operation involves the resection of a portion of rib, usually the eighth rib posteriorly, and the excision of small portions of the pleura. In a series of twenty-one pleural biopsies, Suthif and co-workers found the etiology of the pleurisy by means of pleural biopsy to be tuberculous in seventeen, carcinoma in three and Non-American Blastomycosis in one.

Before concluding the section on operative procedures utilized in the diagnosis of disseminated pulmonary lesions, mention should be made of aspiration needle biopsy and exploratory thoracotomy. In the former operative complications, although in most instances of minor severity, are occasionally serious. In addition, there is the danger of implanting disease in the chest wall by infection or tumor. Moreover, the amount of needle aspirate obtained is often insufficient for diagnostic purposes. For these reasons, needle aspiration of the lung is rarely utilized excepting in instances of massive tumors, usually inoperable carcinomas, in which a definitive diagnosis has not been established. Exploratory thoracotomy is a time-consuming operation associated with considerable morbidity and its use is seldom warranted in the diagnosis of disseminated pulmonary lesions.

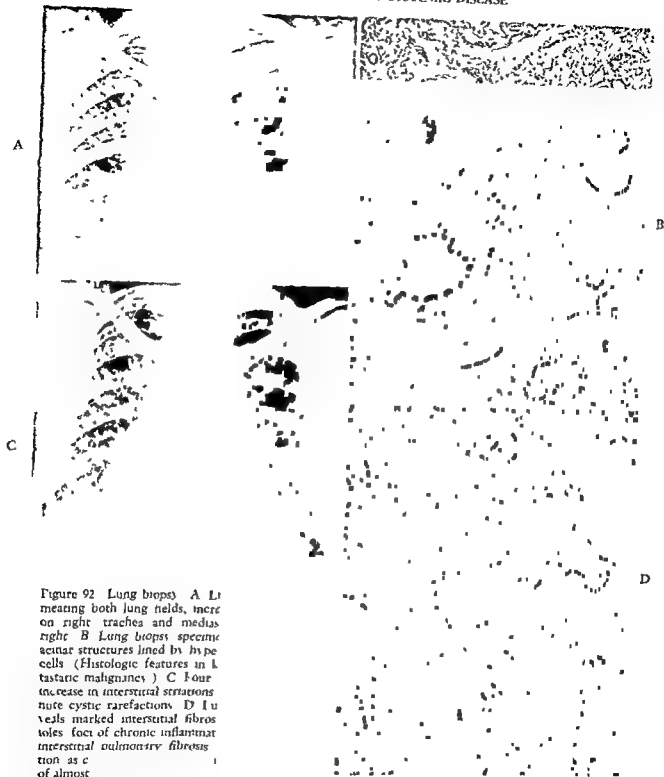


Figure 92 Lung biopsy. A Low magnification both lung fields, increase on right trachea and mediastinum. B Lung biopsy specimen acinar structures lined by hyperplastic cells (Histologic features in metastatic malignancy). C Low magnification both lung fields, increase in interstitial striations note cystic rarefaction. D Low magnification both lung fields marked interstitial fibrosis foci of chronic inflammation interstitial pulmonary fibrosis as cause of almost all respiratory reports. Autopsy revealed emphysema, bronchiolectasis and bronchiectasis (Hamman-Rich syndrome).

LABORATORY AND EXPLORATORY AIDS

Bibliography

WATKINS M M *Clinical Hematology* 3rd Ed Philadelphia Lea & Febiger 1951

EXAMINATION OF SPUTUM

AJELLO L Collecting Specimens for the Laboratory Demonstration and Isolation of Fungi *JAMA*, 146 1581 1951

ISS H E Recent Advances in Knowledge of Fungous Diseases of the Lungs *JAMA*, 144 1041 1950

WILSON H and HOLLEN C Moulds of the Mucous Membranes and Lungs as a Complication of Treatment with Antibiotics Corticotropin and Cortisone *Drugs* 17 9 1954

CLIFF L H and HERBERT P A The Value of Cytological Diagnosis of Pulmonary Malignancy *Am Rev Tuberc* 61 60 1950

COHEN A G Expectoration of Abnormal Substances and Particles Including Parasites *Am J Med* 10 18 1951

ELIAS J A and STEINBERG I Pulmonary Complications of ACTH and Cortisone Roentgen Observations *Radiol* 53 515 1954

FARBER M ROSENTHAL M ALSTON E F BROFF M A and MCGRATH A K Cytologic Diagnosis of Lung Cancer Springfield Thomas 1950

FOOTE N C The Identification of Types of Pulmonary Cancer in Cytologic Smears *Am J Lab* 78 963 1952

JACOBSON J H and ROSE F C Pneumonia Occurring During ACTH and Cortisone Therapy *Tubercle* 36 113 1955

LOVER S VOLA B W SHAE W R NATHANSON L and JACOBI M Diagnosis of Lipoid Pneumonia by Examination of Sputum *Am J Clin Lab* 70 539 1950

MOSBY G S and M QLOON A L *Atlas of Medical Mycology* Baltimore Williams & Wilkins, 1953

PARANICOL G N A Survey of the Activities and Importance of Exfoliative Cytology in Cancer Diagnosis *Ann Int Med* 31 661 1949

WOOLNER L B and McDONALD J R Carcinoma Cells in Sputum and Bronchial Secretions *Surg Gynec & Obst*, 88 773 1949

ZIMMERMAN H M and LUBNER R Tumor Cells in Diagnostic Specimens Their Detection and Significance *W Clin North Am* p 501 April 1949

EXAMINATION OF THE BLOOD

JOSKE R A and KING W F The L E Cell Phenomenon in Active Chronic Viral Hepatitis *Lancet* 7477 1953

LEE S L Clinical Experiences with the L E Cell Test *J Mt Sin Hosp* 27 74 1953

RUBIN F H The Relation of the Erythrocyte Sedimentation and Serum Aref *Int Med* 37 847 1956

RUBIN F H and SMITH N N Relation of Hemoglobin Cell Count and Cell Volume to the Erythrocyte Sedimentation *Arch Int Med* 39 303 1957

SANIS M SCARLATA V and ROBINS H M Laboratory Aids in Diagnosis of the Collagen Diseases *Gynecol* 10 69 1955

WATSON R S and SWIFT S The Significance of a Positive L E Phenomenon *Arch Dermat* 72 103 1955

SKIN TESTS

EDWARDS L B LEWIS I and PALMER C E Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses *Pub Health Rep* 63 1569 1948

FARLOW M L Further Observations on Histoplasmosis *Pub Health Rep* 65 965 1950

JAVEL D G and THOMSON A D The Asheim Test in Sarcoidosis *Quart J Med* 24 49 1953

KLEIM A Preliminary Report on New and Specific Cutaneous Reaction in Boeck's Sarcoid *Nord med* 9 169 1941

ROBINSON A MEYER M and MIDDLEBROOK G Tuberculin Hypersensitivity in Tuberculous Infants Treated with Isoniazid *New England J Med* 252 983 1955

ROGERS F J and HASENHA J R Sarcoidosis and the Asheim Reaction *J Invest Dermat* 23 369 1954

SITZBAUM L E and ELMICH J C The Nickerson Asheim Reaction in Sarcoidosis *Am J Med* 18 790 1954

SMITH D T The Diagnosis and Therapy of Mycotic Infection *Bull New York Acad Med* 29 7 8 1953

SMITH H and BAKER H L KRUH R and BERMAN H Asheim Test in Sarcoidosis and Tuberculosis *J Invest Dermat* 24 353 1953

WILLIAMS R H and NICHOLSON D A Skin Reactions in Sarcoid *Proc Soc Exp Biol & Med* 33 403 1933

CHEST ASPIRATION

CLEGG W L WINFIELD B J O CROWLEY M F, and BLOOM A Diagnostic Value of the Glucose Content of Serous Pleural Effusions *Brit Med J*, 1 1239 1951

KUTNER S K On the Prognosis of Exudative Pleurisy *Acta med scandinav* 97 549 1937

PUDOCK F A The Relationship Between the Specific Gravity and the Protein Content in Human Serous Effusions *Am J Med* 20 569 1941

PHILLIPS S K and McDONALD J R An Evaluation of Various Examinations Performed on Serous Fluids *Am J Med* 21 6 171 1948

PINNEY M and MORRIS G Pleural Effusions *Am Rev Tuberc* 72 121 1950

TINNEY W S and OLNEY A M The Significance of Fluid in the Pleural Space *J Thoracic Surg* 14 448 1945

BRONCHOSCOPY

BENNETT L B and CASTLEMAN B Sarcoidosis with Bronchial Involvement Report of a Case with Bronchoscopy and Pathological Observations *New England J Med* 254 186 1941

LEE W A Bronchoscopy as an Aid in Diagnosis and Treatment of Allergic Pulmonary Disease *Arch Otolaryng* 41 49 1946

OLNEY A M Boeck's Sarcoid Brief Review and Report of Case in which Diagnosis was Made by Bronchoscopic Examination and Biopsy *Ann Otol, Rhin, and Laryng* 55 659 1946

RUBIN M. The Principles of Surgical Treatment in Diseases of the Chest. E. H. Rubin. Philadelphia: Saunders 1947

NEEDLE LIVER BIOPSY

KLATSKIN G., and YESNER R. Hepatic Manifestations of Sarcoidosis and Other Granulomatous Diseases. *Lab J Biol & Med* 23:207 1950

MOREY D. A. J., MANS R. L. and PLEMMER K. Efficacy and Complications of Needle Biopsy of the Liver. *JAMA* 158:1489 1955

RUBIN E. H. and PINNER M. Sarcoidosis. *Ann Rev Tuberc* 49:146 1944

SCADDING J. G. and SHERLOCK S. Liver Biopsy in Sarcoidosis. *Thorax* 3:79 1948

SHERLOCK S. Aspiration Liver Biopsy: Technique and Diagnostic Application. *Lancet* 7:397 1945

VAN BEEK C. and HAY A. J. Aspiration Biopsy of Liver in Mononucleosis Infection and in Bessner Boeck Schaumann's Disease. *Acta med scandinav* 113:123 1943

PRESCALENE LYMPH NODE BIOPSY

CARSTENSEN B., NORRVIK L. and ODENSEN A. Experiences with Retroclavian Lymph Node Biopsy in the Diagnosis of Certain Intrathoracic Diseases. *Dis Chest* 25:443 1954

CONNOR R. G. Prescalene and Deep Cervical Lymph Node Biopsy. *Surg Gynec & Obst* 101:733 1955

CANNONBALL, J. H. Use of Prescalene Lymph Node Biopsy in Absence of Palpable Supraclavicular Nodes: Report of Forty-one Cases. *JAMA* 155:741 1955

DANIELS A. C. A Method of Biopsy Useful in Diagnosing Intrathoracic Diseases. *Dis Chest* 16:360 1949

HARKEN D. E., BLACK H., CLARKE R. and FARRAND R. E. A Simple Cervicomediastinal Exploration for Tissue Diagnosis of Intrathoracic Disease. *New England J Med* 251:1041 1954

SHEETS L. M., TERRILL A. A., and SWINDELL H. Scapular Node Biopsy. *Ann Rev Tuberc* 68:505 1953

STOREY C. F. and REYNOLDS B. M. Biopsy Techniques in the Diagnosis of Intrathoracic Lesions. *Dis Chest* 23:357 1953

LUNG BIOPSY AND OTHER SURGICAL EXPLORATIONS

BLAIR L. G. Disseminated Lung Lesions. *J Fac Radiologists* 6:1 1954

CRAYER L. G., and Binkley J. S. Aspiration Biopsy of Tumors of the Lung. *J Thoracic Surg* 8:436 1939

DUTRA F. R. and GERALD C. L. Needle Biopsy of the Lung. *JAMA*, 151:21 1954

EFFLER D. B., VAN OROSTRAND H. S., McCORMACK L. J. and GANCELO H. A. Lung Biopsy. *Ann Rev Tuberc*, 71:668 1955

FELSON B. Acute Viliary Diseases of the Lung. *Radiology* 59:32 1952

JOHNSON C. R., CLAGETT O. T. and GOOD C. A. The Importance of Exploratory Thoracotomy in the Diagnosis of Certain Pulmonary Lesions. *Surgery* 25:218 1949

KLASSEN K. P., ANGLAN A. J. and CURTIS G. M. Biopsy of Diffuse Pulmonary Lesions. *Arch Surg* 59:694 1949

PRIOR J., KLASSEN K. P. and ANDREWS N. C. Diagnosis of Diffuse Pulmonary Lesions. *Tr Nat Tuberc A* p 109 1951

SCADDING J. G. Chronic Lung Disease with Diffuse Nodular or Reticular Radiographic Shadows. *Tubercle* 33:352 1952

SUTLIFF W. D., HUGHES F. and RICE M. L. Pleural Biopsy. *Dis Chest* 26:551 1954

THEODOS P. A., ALLBRIGHTEN F. F. JR. and BRECHENRIDGE R. L. Lung Biopsy in Diffuse Pulmonary Disease. *Dis Chest* 27:637 1955

Index

A

- Abdominal diseases pulmonary manifestations of 167 178
 - clinical features 14
 - diaphragmatic descent 168
 - Meigs syndrome 16
 - roentgenology 14
- Aneurysm subphrenic 174
- Acanthosis nigricans
 - and malignant neoplasms 193
- Acid fast bacillus see Tubercle bacillus
- ACTH see Steroids
- Acute benign pericarditis and pleuritis 80
- Agammaglobulinemia and pulmonary infections 66
- Agenesis of lungs 735
- Aging population implications in diagnosis 711 717
- Allergic dermatitis 110
 - and Koebner's syndrome 111
 - and pulmonary infiltration 111
 - causes of 111
 - creeping eruption 111
 - erysipelas 111
- Allergic diseases
 - bronchial asthma 9
 - collagen diseases 86
 - diffuse interstitial pulmonary fibrosis 101
 - polyarteritis nodosa 87
 - pulmonary infiltrations and eosinophilia 75
 - and pulmonary lesions 1109
 - rheumatic pneumonia 95
 - rheumatoid disease 96
- Allergy tissue changes in 71
- Amplification of lung 43-47
 - bronchial biopsy in 45 71
 - stimulating pulmonary neoplasm 43
 - types of 43
- Anatomy of chest and contents 779
 - 779
 - bronchi and bronchopulmonary segments 747
 - diaphragm 711
 - hilus 733
 - interlobar fissures 719
 - lungs 734
 - mediastinum 712
 - ribs 779
 - soft structures 779
 - terminal lung radicles 741
 - thoracic cage 779

- Anemia
 - in diagnosis 269
 - in hiatus hernia 231
 - in idiopathic pulmonary hemosiderosis 58
 - in malignant neoplasms 54
 - sickle cell and pulmonary lesions 54
 - in tuberculosis 53
- Angiocardiology 253
- Animals of lungs development 715 239
 - agenesis 735
 - azygos lobe 236
 - bronchovascular 237
 - inferior accessory lobes 737
 - situs inversus and bronchiectasis (Hartnager's syndrome) 233
- Annoxa 725
- Anteroposterior projection in roentgenography 750
- Armed services personnel x-ray surveys 8
- Arteries of lungs
 - bronchial 179
 - pulmonary 179
- Arteriosclerosis pulmonary 197
 - and hypertension 197
 - primary 197
 - secondary 197
- Arteriovenous aneurysm of lung see Cavernous hemangioma
- Aspiration (see also chest aspiration)
 - importance in history 774
 - pneumonia 179
- Asthma
 - bronchial 9
 - cardiac 194
- Atelectasis
 - in bronchial asthma 74
 - postoperative 175
 - prevention of 14
- Atypical amyloidosis 48
- Auscultation of chest 277
- Azotemia and pulmonary lesions 196
 - 194
- Azotemic lung 196
- Azygos lobe 236
 - vein obstructed in 231

B

- Bat's wing shadows see Azotemia
- Biopsy bronchoscopic 71
 - in amyloidosis 45
 - of bone marrow 111
 - of liver 157
 - of lung 107 276 277
 - of lymph node 17
 - in sarcoidosis 157
 - of skin 157
- Blood circulation of lungs 189
 - vertebral 181
- Blood diseases and pulmonary lesions 52 70
 - hemorrhagic 61
 - hemosiderosis 57
 - in infectious mononucleosis 66
 - leukemoid reactions 61
 - in malignant neoplasms 53
 - myeloma 65
 - polycythemia 67
 - sickle cell anemia 54
 - in tuberculosis 52
- Blood examination 768 770
 - cytological 269
 - eosinophilia causes of 769
 - erythrocyte sedimentation 768
 - E.T. test 269
- Blood vessels
 - aberrant pulmonary 717
 - lymphatic 181 276
 - pulmonary 179
 - thrombi 180
 - systemic 179
- Body section roentgenography (tomography) 251
- Bone disease
 - and metastatic calcification 48
 - and metastatic malignancy 184
- Boston chest x-ray survey 5
- Bronchi 742
- Bronchial asthma 71 74
 - atelectasis in 74
 - pneumothorax spontaneous in 74
 - roentgenology 71
- Bronchiography 257
- Bronchopulmonary segments 747
- Bronchovesicular
 - and biopsy 271
 - in systemic diseases 273
- Bronchovascular anomalies 217 719
 - extralobar 238
 - intralobar 237
- Butterfly shadows, see Azotemia

C

calcinosis
 and metastatic calcification 47
 in sarcoidosis 157
 in scleroderma 135
 carcinoma of lung
 and *acanthosis nigricans* 143
 case finding 5
 curability 5
 and dermatomyositis 141 142
 metastatic 178 187
 and osteoarthropathy 18
 and peripheral neuritis 129
 and scleroderma 134
 and skin diseases 135 139 142
 radiopulmonary dynamics 189
 rhabdospasm *see* Megacystophagus
 radiovascular diseases
 xeroderma 196
 cavernous hemangioma of lung 201
 in thorax 200
 pulmonary arteriosclerosis 197
 congestion and edema 191
 dynamics 189
 embolism and infarction 203
 and pulmonary manifestations 189
 210
 case finding *see* X ray surveys
 cavernous hemangioma of lung 201
 in thorax 200
 resection of 201
 roentgenology 202
 anastomosing scene in diagnosis 211 220
 and character of diseases 212
 fashions in medicine 211
 and forms of treatment 212
 and Man made diseases 213
 est aspiration 272 273
 or fluid 272
 pain
 and periodic disease 224
 causes of 224
 painful areas 223
 physical exploration 276
 or pleural biopsy 279
 roentgenography *see* X ray of
 chest X ray surveys
 tonic pneumonitis
 of cholesterol type 32
 nical history 213 217
 nics
 Morrisania City Hospital 14
 pneumonia in 15
 prenatal chest x rays in 14
 routine chest x rays in 14
 tuberculosis in 15
 clubbing *see* Digital clubbing
 collagen diseases
 dermatomyositis 139
 diffuse interstitial fibrosis of lungs
 101

disseminated lupus erythematosus

114

erythema nodosum 113
 increasing incidence of 213
 interrelationship of 86
 polyarteritis nodosa 87
 rheumatic pneumonia 95
 rheumatoid arthritis 96
 rheumatoid diseases 96
 scleroderma 135
 Community chest x ray surveys 3 17
 Concomitant lung diseases 21
 Congestion and edema pulmonary,
 193 196

causes of 194
 morphologic classification 196
 physiological considerations 193
 roentgenology 194

Contrast techniques in roentgenology
 graphy 252 253
 angiocardiology 251
 barium meal 252
 bronchography 252
 diagnostic pneumoperitoneum 252
 diagnostic pneumothorax 252

Citronine *see* Steroids

Cough and wheezing 227

emesis 227

syncope 221

Cyanosis

in cavernous hemangioma 207
 and dyspnea 225

Cystic fibrosis of pancreas

(mucoviscidosis)

etiology 25
 incidence 26
 pathology 25 27
 and pulmonary infections 25 29
 roentgenology 27
 tests for 26
 treatment 28

Cytology exfoliative 267

of blood 269

of sputum 265 267

D

Dermatitis *see* Allergic dermatitis

Dermatomyositis 139-142

and collagen diseases 140
 and malignant neoplasms 141
 pulmonary lesions 140 141

Developmental anomalies *see* Anomalies of lungs developmental

Diabetes and pulmonary infections

21 25

nontuberculous infections 23

diabetic gangrene 23

suppurative pneumonia 23 24

tuberculous infections 22

diabetic phthisis 22 27

roentgenology 24 25

treatment 23

Diagnosis 211 218

changing character of diseases 212

fashions in medicine 211

forms of treatment 212

population 211

scene 211 220

clinical history, 213

laboratory and exploratory aids in
264 282

physical exploration 226

physical x ray examination 217

pitfalls in 256 263

roentgen 229 255

symptoms in 221

Diaphragm and diseases of 167 174

bulgings of 169 231

displacements 167

eventration 167

herniation 170

hiatus 170 231

incidence of 172

roentgenology 172

Kienbock phenomenon 169

and Meigs syndrome 177

openings in 231

paralysis 168

pleurisy 172

in systemic diseases 173

with effusion 173

roentgenotomy 231

tumors 169

Diffuse interstitial pulmonary fibrosis

see Interstitial pulmonary

fibrosis

Digital clubbing 18

causes of 19 20

in cavernous hemangioma 207

in interstitial pulmonary fibrosis 101

in malignant neoplasms 19

in pulmonary suppurations 19

Diseases *see* Table of contents

Disseminated lupus erythematosus *see*

Lupus erythematosus

Dyspnea

and cyanosis 223

etiological classification 225

E

Effusion pleural 272

eosinophilic 29

hemorrhagic 61

in thorax 200

Embolism and infarction 203 207

clinical features, 205

differentiated diagnosis 206

etiological considerations 203

incidence 205

and phlebotomiasis 205

roentgenology 206

Fleischer lines 207

Enlargement pulmonary *see* Metastatic diseases of lungs

INDEX

Extralobar sequestration *see* Sequestration

F

Fasciitis
and allergic dermatitis 111
causes of 269
in allergic diseases 73
in malignant neoplasms 53
and severe pulmonary infiltrations 79
in systemic diseases 769
and transitory pulmonary infiltrations 76
tropical pulmonary 82
Eosinophilic granuloma 34-43
of bone 39
of lung 40
"honeycomb" lungs 40
spontaneous pneumothorax in 47
pathology 40
roentgenology 41
rurs in roentgen diagnosis 257 262
inherent 267
extrinsic 257
latent period 237
number and size of infiltrations 258
site of disease 259
reactive 760
between reader variability 261
negative vs positive chest x rays 260
results 261
within reader variability 261

Erythema multiforme
and pneumonia 117
Erythema nodosum 111
and hypersensitivity 113
causes 111 114
intrathoracic lesions 113
Erythrocyte sedimentation test 768
Esophagus diseases of
in aspiration pneumonia 169
and elevation of diaphragm 169
megaesophagus, 169
in scleroderma 135

Ethnic groups
tuberculosis in 9
Elevation *see* Diaphragm
Exfoliative cytology 267 768
criteria of malignancy 768
false positive results 768
in carcinoma of lung 767
Exocrine glands
in cystic fibrosis of pancreas, 25
Expectoration 772
Exploratory aids 772 280
biopsy of liver needle 773
lung, needle 279
pleura 279
prevalence lymph node 276
bronchoscopy 773
chest aspiration 272
thoracotomy 279

G

Fashions in medicine 211
Fibrosis cystic of pancreas 25
interstitial pulmonary 101
Fluoroscopy 249
Fungal diseases
differential diagnosis 267
tests for 265 771 272

H

Gaucher's disease 35
roentgenology 41
General hospitals
results 10 12 13
and routine chest x rays 9
Glomerulonephritis acute
in collagen diseases *see* Renal disease
Granulomas
allergic 97
in liver biopsy 157
sarcoid 148 150
Weener's 91

I

Hanman Rich syndrome *see* interstitial pulmonary fibrosis
Hand-Schuller Christian's disease
pathology 37
and pulmonary lesions 37
roentgenology 41
Heart disease
and chest x ray surveys 6
and film interpretation 7
Heerfordt's disease *see* Uveoparotid fever
Hemoptysis
causes of 273
in diagnosis 272
Hemorrhagic diseases
and pulmonary lesions 63
Hemosiderosis *see* Pulmonary Hemosiderosis
Hepatoplenomegaly *see* Collagen diseases Histiocytosis
Sarcoidosis
Hernia of diaphragm *see* Diaphragm
Hirschsprung's 170 731
Hilus 233
Histocytosis
endogenous lipid pneumonia 32
eosinophilic granuloma of bone, 39
eosinophilic granuloma of lung 40
Gaucher's disease 35
Hand Schuller Christian's disease 37
Letterer-Siwe's disease 37
Niemann-Pick's disease 35
and pulmonary lesions, 31-43
roentgenology 41
treatment of 41

History taking 713 717
and age of patient 217
in diagnosis, 214
in occupational diseases 217
psychosomatic aspects 217
techniques, 214
"Honeycomb" lungs 40 41
spontaneous pneumothorax in 47
Hydralazine syndrome 213
Hypothorax
and cardiac disease 700
causes of 200
and Meigs syndrome 177
roentgenology 201
Hyperparathyroidism
and metastatic calcification 47
Hypersensitivity (*See also* Allergic diseases)
angitis 97

Hypertension on pulmonary 190
Lanes B of Kety 191
physiological considerations 190
roentgenology 191
Hypertrophic pulmonary osteoarthropathy 18 21
causes of 19 20
definition of 18
digital clubbing in 18
and malignant neoplasms 19
and pituitary gland 20 21

J

Idiopathic pericarditis and pleuritis, 80
pleurisy with effusion 272
pulmonary hemosiderosis 58
Inclusion bodies 149 150
Infectious mononucleosis
and pulmonary lesions 65 67
Inferior accessory lobes 237
Inherent errors
in roentgen diagnosis 767
Inspection of chest 226
Interlobar fissures 239
fluid in 739
sequestration 217

Interstitial pulmonary fibrosis
causes of 107
and collagen diseases 101
diffuse 101 105
digital clubbing in 18
and Hanman Rich syndrome 101
and hypersensitivity 107 104
lung biopsy in 102
and scleroderma 137 138
treatment of 103
Intralobar sequestration 217
surgical considerations, 218 239
intrinsic errors
in roentgen diagnosis, 257
Iron overload
and bil

- and pulmonary hemosiderosis 60
roentgenology 61
- J**
- Jackson Huber classification of bronchopulmonary segments 242
- Jungling's disease 154
- K**
- Kartagener's syndrome *see* *Sinus In*
versus and bronchiectasis
- Kienbock phenomenon 169
- Kveim skin test
in sarcoidosis, 158
technique 271
- L**
- Laboratory aids 264 272 (*See also* *Ex*
ploratory aids)
examination of blood 268 270
sputum 264 268
skin tests 270 272
- Lateral projections
in roentgenography 260
- L E test 269
false positive 269
in hydralazine syndrome 213
in lupus erythematosus, 116
in rheumatoid diseases 97
- Letterer-Siwe's disease 3"
roentgenology 41
- Leukemia
intrathoracic lymphoma 64
and pleural effusion 65
and pulmonary lesions 63
roentgenology 64
- Leukemoid reactions
in malignant neoplasms 53
in tuberculosis 52
- Lines in chest x ray
B of Kerley 195
causes of 197
Fleischner 207
- Lingula of left upper lobe 245
- Lipid pneumonia
aspiration 12 214
endogenous 32
roentgenology 33
simulating carcinoma 33
- Lithiasis of pancreas
microlithiasis of lungs 58
and pulmonary lesions 71
- Liver aspiration needle biopsy 273
274
enlargement *see* *Hepatosplenomeg*
aly
- Loeffler's syndrome *see* *Pulmonary*
infiltrations and eosinophilia
- Lordosis projection in roentgeno
graph 250
- Los Angeles chest x ray survey 4 5
- Lung biopsy 102 276
fissures 233
- in systemic diseases 44
shadowy 277
terminal radicles of 241
- Lupus erythematosus 114 121
clinical features 115
definitions 114
I E test 115
pathology 116 117
pulmonary lesions, 116
roentgenology 118
- Lymphatics pulmonary
anatomy 276
- Lymph nodes
biopsy 276
intrathoracic 232
in metastatic diseases 181
presclerotic 276
in sarcoidosis 159
- Lymphomas intrathoracic 64
- M**
- Man made diseases, 213
- Mediastinum 217 233
- Medical students and nurses
chest x ray surveys in 8
tuberculosis in 8
- Megacosophagus 169
- Melars syndrome 176
causes 176-178
treatment 178
- Mental institutions
chest x ray surveys in 9
tuberculosis in 9
- Metabolic diseases
amyloidosis 43
cystic fibrosis of pancreas 23
diabetes 21
histiocytosis 31
hypertrophic pulmonary osteoar
thropathy 18
metastatic calcification 47
and pulmonary lesions 18 51
- Metastatic calcification of lungs 47 50
and bone diseases 48
and excessive alkali intake 48
and hyperparathyroidism 47
and hypernatremosis D 48
and renal disease 47
- Metastatic diseases of lungs, 178 188
diagnosis 185 187
embolization pulmonary 180
selective localization techniques 187
vascular channels 181
malignant neoplasms 181 187
metastatic calcification 47
primary sites 184
roentgenology 181 185
- Microtheliasis pulmonary 58
- Mikulicz syndrome
and sarcoidosis 157
- Milk and alkali excessive intake
and metastatic calcification 48
- Minneapolis chest x ray survey 4
- Miscellaneous diseases
in chest x ray surveys 7
- Mitral stenosis
and heart disease case finding 6
and hydrothorax 200
and lines B of Kerley 191
and pulmonary arteriosclerosis, 197
and pulmonary congestion and
edema 193
and pulmonary hemosiderosis 5"
and pulmonary hypertension 190
191
- Mononucleosis *see* *Infectious mono*
nucleosis
- Morrisania City Hospital
routine admission chest x rays 10
- Mucous membrane diseases, *see* *Skin*
diseases
- Mucosoidosis *see* *Cystic fibrosis of*
pancreas
- Multiple (multiphasic) screening 7
advantages and disadvantages 8
procedures included 8
results, 8
- Myasthenia gravis
and bronchiogenic carcinoma 179
- Mycosis fungoides
and pulmonary lesions 121
- Mycoma 65
and recurrent pneumonia 60
- N**
- Needle aspiration *see* *Chest aspira*
tion
- Negative chest x ray
pitfalls in diagnosis 2 7
reliability of 7
- Neoplasms pulmonary (*See also* *Meta*
static diseases of lungs)
in chest x ray surveys 5 6
- Neurocutaneous diseases
and pulmonary lesions 127 130
- Neurofibromatosis, 126
intrathoracic 127
- Neurogenic tumors 128 129
- Niemann Pick's disease
and pulmonary lesions 35 41
- Normal chest 256 257
- O**
- Oblique projections
in chest roentgenography 250
- Occupational lung diseases
and history taking, 217
- Oltun University health service
and routine chest x rays 3 4
- Osteoarthropathy hypertrophic pul
monary *see* *Hypertrophic pul*
monary osteoarthropathy
- P**
- Pain in chest *see* *Chest pain*
- Palpation of chest 276

- Pancreatic disease
lithiasis 21
and pulmonary lesions, 25, 175
pathways of pulmonary metastases 178 180
- Pituitary gland
and intrathoracic lesions, 175
and Meigs syndrome 176
and metastatic disease 181
- Penetration techniques
in chest roentgenography 251
Percussion of chest 276
Periodic disease 224
Peripheral neuritis
and bronchiogenic carcinoma 179
- Phlebography 233
Photofluorography
in chest x ray surveys 3 10
Physical exploration of chest 26
Physical x ray examination 71 70
Pitfalls in roentgen diagnosis 257 63
inherent errors, 76
intrinsic errors, 75
subjective errors 760
- Pituitary gland
and hypertrophic pulmonary
osteoarthropathy 70 71
- Planigraphy (tomography) 71
- Pleural effusion
in abdominal diseases 175
differential diagnosis 71
in Meigs syndrome 176
physical diagnosis of 727
- Pleurisy
diaphragmatic 171
with effusion 173
- Pneumonia
diagnosis of 17
eosinophilic 76
lipid 32
rheumatic 95
Pneumoperitoneum
diagnostic 71 71
in pulmonary emphysema 71
- Pneumothorax
diagnostic 25
spontaneous
in bronchial asthma 71
in cystic lung 47
- Polycythemia
clinical features 88
epidemiology 88
pathogenesis, 88
pathology 88 90
and pulmonary lesions 90
roentgenology 91
treatment 91
- Polycythemia
in anoxia 67
in cavernous hemangioma of lung 201
- in pulmonary arteriosclerosis 193
in tuberculosis 53
- Population groups (See also X ray
surveys)
aging implications of, in diag-
nosis 211 217
- Postero-anterior projection
in roentgenography 250
- Pre operative chest x ray 9
- Prescalene lymph node biopsy 276
- Primary amyloidosis 41
- Private practitioner
and routine chest x rays 15
- Progressive systemic sclerosis see
Scleroderma
- Projection techniques
in roentgenography 750
- Psychosomatic aspects
of pulmonary disorders 21
- Pulmonary hemosiderosis
idiopathic 58
and iron overload 60
and mitral stenosis 60
infiltrations and eosinophilia 75 83
Loeffler's syndrome 76
and parasitic infestations 87
and polyarteritis nodosa 78
tropical 87
and vascular allergy 79
- Neoplasms
osteovarthropathy see Hypertrophic
pulmonary osteoarthropathy
- R
- Railrocks of lung terminal 241
- Rai naud's phenomenon
and scleroderma 135
- Renal disease
and azotemic lung 196
and collagen diseases 87
and metastatic calcification 47
- Rheumatic heart disease
pneumonia 95
and pulmonary hemosiderosis 58
- Rheumatoid disease
and collagen diseases 86
and diffuse interstitial pulmonary
fibrosis 101
and Hamman Rich syndrome 101
- Pleuro-pulmonary lesions in 96 101
- Ribs 719
cervical 230
- Right middle lobe 243
syndrome 243
- Roentgen techniques 249
- Roentgenography techniques 750
contrast 257
penetration 251
projection 250
- Sarcoidosis 147 166
diagnosis, 151
epidemiology 150 151
incidence and distribution 14
inclusion bodies 147 150
intrathoracic 158
Jungling's disease 144
Kveim skin test in 158
laboratory findings in 156
and metastatic calcification 48
Mikulicz syndrome 152
pathology 149
pulmonary lesions in 159
roentgenology, 159
tissue examination in 157
treatment 161
tuberculin reaction in 155
and tuberculosis 150
unexplained fever 152
Schaumann inclusion bodies
in sarcoidosis 149
- Scleroderma
and pulmonary lesions 144
Sclerodermia
and aspiration pneumonia 137
calcinosis in 135
and carcinoma of lung 114
and collagen diseases 136
and interstitial pulmonary fibrosis 138
pathology 135
and pulmonary lesions 135 139
and Rai naud's phenomenon 137
roentgenology 137
- Secondary lung disease vii
- Selective localization
of pulmonary emboli 182
- Sequestration
ectoplastic 237
intralobar 237
- Sickle cell anemia
and pulmonary lesions 54
- Situs inversus and bronchiectasis 235
- Sjogren's disease and pulmonary
lesions 144
- Skin diseases and pulmonary lesions
110 166
acanthosis nigricans, 142
allergic 110
dermatomyositis, 139
disseminated lupus erythematosus 114
erythema multiforme 112
erythema nodosum 113
and internal diseases 110
and malignant tumors, 114 135, 139
147
mycosis fungoides, 121
neurocutaneous 177
sarcoidosis

scleredema 144
 scleroderma 135
 Sjogren's disease 144
 Skin tests 270-272
 in fungous diseases, 272
 Kveim 158 271
 tuberculin 155 270
 Soft structures of chest 230
 Sputum examination 264 268
 effect of treatment 265
 exfoliative cytology 267
 for foamed particles 265
 for fungi and parasites 265
 for tubercle bacilli 264
 Stellate inclusion bodies
 in foreign body reaction 150
 in sarcoidosis 149
 Steroid treatment
 of allergic diseases 71 83 93 119
 of histiocytosis 41
 of interstitial pulmonary fibrosis 103
 of sarcoidosis, 161
 Subjective errors
 in roentgen diagnosis 260
 Subphrenic abscess 174
 Superior segments of lower lobes 245
 Superior vena caval obstruction 232
 Suppuration pulmonary
 and cystic fibrosis of pancreas 25
 and diabetes 21
 and hypertrophic osteoarthropathy 18
 Symptoms in diagnosis 223 228
 Sweat test for cystic fibrosis of pancreas 26

T

Tests *see* Laboratory aids
 Thoracic cage 229
 Thoracotomy exploratory 229
 Thrombocytopenia
 in tuberculosis 53
 Tissue changes
 in allergy 71
 Tomography (planigraphy) 251
 Treatment (*See also* individual diseases)
 changing forms 212
 masking effect *cf* 265
 Tropical pulmonary eosinophilia 82
 Tuberculin skin tests
 in diagnosis 156 20 271
 Tuberculosis
 and erythema nodosum 113
 and lupus erythematosus 118
 pulmonary
 and diabetes 22
 in chest x ray surveys 3 4 5
 and sarcoidosis 150
 and unusual blood findings 52 53
 Tuberculous sclerosis
 and pulmonary lesions 123
 Tumors of lung (*See also* Carcinoma of lung)
 and myasthenia gravis 129
 and skin diseases, 134
 and unusual blood findings 53

U

United States Public Health Service
 and chest x ray surveys 3
 Uremia *see* Azotemia
 Uveiparotid fever
 and sarcoidosis 152

V

Vascular, lung, 73
 Vascular anomalies of lung 237
 Vena caval obstruction
 causes of 232 233
 Vertebral blood circulation
 and metastatic disease 181
 Vitamin D intoxication
 and metastatic calcification 48
 Von Recklinghausen's disease *see*
 Neurofibromatosis

W

Wepener's granulomatosis 91

X

X ray of chest
 anatomical considerations, 229 235
 as a mirror of systemic diseases 24
 normal 256
 pitfalls in diagnosis 257 262
 preoperative 14
 and practice practitioner 15
 X ray surveys
 cancer case finding 5
 heart disease case finding 5
 mass 3 8
 multiple (multiphasic) screening 7
 of selected population groups 8
 armed service personnel 8
 in clinics 14
 in general hospitals 9
 of inmates of mental institutions, 9
 cf medical students and nurses, 8
 cf pre employment groups 9
 cf vulnerable ethnic groups 9
 tuberculosis case finding 3

This Book
***The Lung as a Mirror of
Systemic Disease***

By

ELIH RUBIN MD

was set printed and bound by the Pantagraph Printing and Stationery Company of Bloomington Illinois. The engravings were made by the Capitol Engraving and Electrotype Company of Springfield Illinois. The page trim size is 8 1/2 x 11 inches. The type page is 39 x 54 picas. The type face is Janson set 11 point on 12 point. The text paper is 70 lb Art Gloss. The cover is Bimcroft's Buckram 1910.



With THOMAS BOOKS careful attention is given to all details of manufacturing and design. It is the Publisher's desire to present books that are satisfactory as to their physical qualities and artistic possibilities and appropriate for their particular use. THOMAS BOOKS will be true to those laws of quality that assure a good name and good will.

